Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Sevelamer hydrochloride

Proprietary Product Name: Sevelamer GPPL, Sevelamer GxP, Seveligand, Phosligand, APO-Sevelamer, APOTEX-Sevelamer, Chemmart Sevelamer, GenRx Sevelamer, Terry White Chemists Sevelamer

Sponsor: Generic Partners

November 2015

Updated July 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

AE	Adverse Events
ARGPM	Australian Regulatory Guidelines for Prescription Medicines
ARTG	Australian Register of Therapeutic Goods
^{o}C	degrees Celsius CI
CI	Confidence Interval
CKD	chronic kidney disease
CMI	Consumer Medicine Information
CV	coefficient of variation
EPAR	European Public Assessment Record
EU	European Union
FDA	Food and Drug Administration
GFR	glomerular filtration rate
g	gram
HC	Health Canada
HCl	hydrochloric acid
HD	haemodialysis
HAS	Health Sciences Authority (Singapore)
iPTH	intact parathyroid hormone
kD	kiloDalton
KDOQI	Kidney Disease Outcomes Quality Initiative
kg	kilogram
m^2	square metre
mEq	milliequivalents
mg	milligrams
MHRA	Medicines and Health Regulatory Agency
min	minute

AE	Adverse Events
mm	millimetres
mM	millimolar
mmol	millimols
mL	millilitre
L	litre
PD	peritoneal dialysis
PI	Product Information
pg	picogram
rpm	revolutions per minute
SD	standard deviation
tds	ter die sumendum (three times daily)
TGA	Therapeutic Goods Administration
TGO	Therapeutic Goods Order
T/R	test to reference ratio
US(A)	United States of America
µm	micrometre

I. Introduction to product submission

Submission details

Type of submission:	New generic
TGA decision:	Rejected
Date of initial TGA decision[1]:	13 February 2015
Date of final TGA decision:	30 June 2015
AAT outcome*	Appeal was withdrawn[2]
Active ingredient(s):	Sevelamer hydrochloride
Product name(s):	Sevelamer GPPL, Sevelamer GxP, Seveligand, Phosligand, APO-Sevelamer, APOTEX-Sevelamer, Chemmart Sevelamer, GenRx Sevelamer, Terry White Chemists Sevelamer
Sponsor's name and address:	Generic Partners Pty Ltd, 191 Riversdale Rd, Hawthorn VIC 3122
Dose form(s):	Film coated tablet
Strength(s):	800mg
Container(s):	High Density Polyethylene (HDPE) bottles and Foil blister packs.
Pack size(s):	180 tablets in bottle; 30 or 180 tablets in blister pack
Approved therapeutic use:	Not applicable.
Route(s) of administration:	Oral (PO)
Dosage:	Not applicable
ARTG number (s):	Not applicable

*AAT= Administrative Appeals Tribunal

Product background

This AusPAR describes the application by Generic Partners Pty Ltd to register the first generic sevelamer product of the reference product Renagel by Genzyme Australasia Pty Ltd which contain 800 mg of sevelamer hydrochloride. The application originally also included a 400 mg strength tablet but this was withdrawn. Therefore this submission is to register only the 800 mg tablet as a generic product.

Sevelamer is indicated for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease (see below). It acts by binding phosphate in the dietary tract, thereby lowering the phosphorus concentration in the serum. Sevelamer decreases the incidence of hypercalcaemic episodes as compared to patients using calcium

[1]The initial Delegate's decision was reviewed in accordance with section 60(4) of the *Therapeutic Goods Act1989*. For further details see the *Final Outcome* section of this AusPAR.
[2] The sponsor appealed to the AAT for a review of the TGA's decision not to register Sevelamer.

based phosphate binders alone, probably because the product itself does not contain calcium. Sevelamer treatment also results in a lowering of low-density lipoprotein (LDL) and total serum cholesterol levels by increasing faecal excretion of bile acids.

The sponsor has proposed the same indications as for Renagel:

> *Sevelamer is indicated for the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease.*

The proposed dosage is also the same as that for Renagel:

> *The recommended starting dose for patients not taking a phosphate binder is 800 to 1600 mg, which can be administered as one to two sevelamer 800 mg tablets with each meal based on serum phosphorus level.*
>
> *Additional dosing instructions are provided for patients switching from calcium acetate to sevelamer and for dose titration of sevelamer based on serum phosphorous levels with the goal of lowering serum phosphorous.*

Australian regulatory guidance

TGA guidelines

- Schedule 9 of the Therapeutic Goods Regulations 1990 Part1 1 Interpretation of table Section 1(1) - definition of a generic product
- Australian Regulatory Guidelines for Prescription Medicines Appendix 15
  - Section 2: Products for which biopharmaceutic data are not normally required
  - Section 4: Justification for not submitting biopharmaceutic data
  - Section 7: Choice of the reference product for bioequivalence of generic medicines
- Therapeutic Goods Order No. 78 – Standard for Tablets and Capsules (29/10/2008) Subsection 11(b)

TGA adopted EU Guidance:

- Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev1)
- Clinical Requirements for Locally Applied, Locally Acting Products, containing Known Constituents (pp 193 – 198 of Rules 1998(3C) – 3CC12a

In addition to the above guidelines, the sponsor has cited FDA guidance in this submission that is specific to sevelamer and the biopharmaceutic studies required for a generic product. The sponsor refers to a guidance version issued in August 2010 however the current version was issued in August 2011.

- FDA Draft Guidance on sevelamer hydrochloride, August 2011:

Regulatory status

This is an application for a new generic. The innovator product, Renagel, received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 28 June 2005.

At the time the TGA was considering this application, a similar application had been approved in Uruguay (2013) and India (2007) for *Phosphate-binding agent prescribed for hyper-phosphataemia* and was being considered in Germany.

An application for Sevelamer carbonate is being considered in the USA.

II. Quality findings

Introduction

Sevelamer hydrochloride is not systemically absorbed and consequently no biopharmaceutic studies were provided with the submission. Neither have clinical equivalence studies comparing the proposed and innovator products been conducted. Rather, studies were conducted in which the in vitro phosphate binding capacity of the proposed and innovator products were compared.

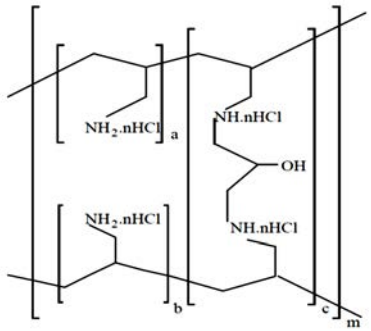
Sevelamer hydrochloride and sevelamer hydrochloride tablets are not subject to British Pharmacopeia (BP) or US Pharmacopeia (USP) monographs; however draft USP monographs are available for both the drug substance and drug product.

Due to the complexity and nature of the drug substance, the quality control tests and limits applied to the drug substance play an important role in establishing that the drug substance in the proposed generic product is the same as that in the innovator product. The limits proposed for some quality control tests for the drug substance in the proposed generic product are different to those in the draft USP monograph.

Drug substance (active ingredient)

Sevelamer hydrochloride (HCl) (see structure below) is an insoluble and non-absorbed ion-exchange resin that reduces serum phosphorus concentrations.

Figure 1: Sevelamer HCl structure



a, b =number of primary amine groups (a+b = 9)
c = number of cross linking groups (c = 1)
n = fraction of protonated amines (n = 0.4)
m = large number to indicate extended polymer network

It contains multiple amine groups separated by one carbon from the polymer backbone. These amines become partially protonated in the intestine and interact with phosphate molecules through ionic and hydrogen bonding. The extent of cross-linking in the drug substance is very sensitive to the manufacturing conditions and this makes it difficult to match the relevant therapeutic properties of the drug substance between different manufacturers.

Key aspects of the drug substance quality control are the tests and limits applied: identification; phosphate binding capacity; chloride content; swell index; total titratable amines; water soluble oligomers; allylamine content; epichlorohydrin content and particle size. The limits for phosphate binding capacity and total titratable amines are akin to assay tests whilst the tests for water soluble oligomers, allylamine content and epichlorohydrin give an indication of impurity levels in the drug substance.

The limits and tests for identification, chloride content, water soluble oligomers, allylamine content, epichlorohydrin content and particle size are in line or tighter than those specified in the draft USP monograph for sevelamer hydrochloride. All of the tests have been adequately described and were adequately validated.

The level of total titratable amines in the drug substance is a surrogate assay parameter and also provides an indirect measure of its phosphate binding capacity. The most recently proposed titratable amine limit for the drug substance (and drug product) is 9.6-12.9 mmol/g.[3]. The proposed limit is looser that that specified in the draft USP drug substance monograph. This indicates that the proposed drug substance may have fewer free amine sites compared with the innovator drug substance capable of functioning in an ion-exchange capacity.

In the company's response to the TGA's Pharmaceutical Subcommittee (PSC) minutes a comparison of the total titratable amines and phosphate binding capacity of the drug substance used in the proposed and innovator products was provided.

If any conclusion can be drawn from this information it may be that the proposed drug substance has marginally fewer free amine sites as compared with the innovator drug substance capable of functioning in an ion-exchange capacity.

The titratable amines levels are reflected in the phosphate binding capacities of the drug substance. The phosphate binding capacity of the proposed drug substance is 5.15 to 5.89 mmol/g (5.39 mmol/g),[4] whereas the values for the innovator drug substance show levels twixt 5.62 and 6.00 mmol (average 5.81 mmol/g). The differences might appear marginal, however in the absence of an acceptable phosphate binding study and a clinical study using the proposed generic, these may impact on the efficacy of the proposed generic product.

The swell index of the drug substance is proportional to the extent of cross-linking, which is inversely related to the free amine content. The free amine content is directly related to the drug substance phosphate binding capacity. Consequently, the swell index limit for the proposed drug substance should be aligned with the limit for the innovator product. The most recently proposed swell index limit for the drug substance is 6.9 to 9.4. The limit specified in the draft USP monograph is 6.2 to 8.4.[5]

The company states that the differences between the proposed drug substance and innovator drug substance do not lead to differences in the phosphate binding capacities. The draft USP sevelamer hydrochloride monograph does not include a limit for this parameter, however the company's most recently proposed limits in the drug substance and drug product specification (5.2 to 6.2 mmol/g) are close to what the TGA has previously indicated would be acceptable (5.2 to 6.4 mmol/g).

Drug product

A conventional wet-granulation immediate release formulation is proposed. The active represents about 71% of the total tablet weight and the other excipients include mannitol, purified water, ethyl cellulose, silica, stearic acid and a clear Opadry film coating. The manufacturing process follows the steps: drug substance hydration; wet granulation (with isopropyl alcohol), milling, blending, compression and aqueous film coating.

[3]The sponsor later agreed to comply with the draft USP specification in their pre-ACPM response (see *Response from sponsor* page 41 below).
[4]The sponsor later agreed to comply with 5.2 to 6.4 mmol/g in their Pre-ACPM response (see *Response from sponsor* below).
[5] The sponsor agreed to comply with the USP monograph limit in Pre-ACPM response (see *Response from sponsor* below).

The quality of the drug product is controlled by a specification that includes appropriate limits for average tablet weight and uniformity of weight as well as residual solvent (isopropyl alcohol) and disintegration. Impurities are controlled by the limit for soluble oligomers and the limit for allylamine and these are in line with those specified in the draft USP monograph.

The limits most recently proposed for the key parameters that are predictive of the ability of the drug product to bind phosphate (free amine level and phosphate binding capacity) have been matched to the corresponding limits in the drug substance.

Accelerated and long-term stability data were provided to support the proposed shelf life of 24 months for the unopened product when stored below 25ºC and protected from moisture. No photo stability testing was conducted and consequently the sponsor will be asked to include a 'protect from light' instruction on the labels and in the PI. Appropriate in-use stability data were provided for the HDPE bottle presentations.

In vitro comparison between the proposed and innovator products

Sevelamer hydrochloride is not systemically absorbed and consequently no bioequivalence studies were performed for the proposed product.

An equilibrium and kinetic in vitro phosphate kinetic study (ARL/E11/R01) was conducted which examined the proposed 800 mg tablets with an innovator reference product (800 mg Renagel sevelamer hydrochloride). The use of an overseas reference product is considered acceptable in this instance.

The equilibrium binding portion of the study was conducted by incubating the test and reference products for 2 hours at 37ºC with eight different phosphate concentrations (1 mM to 40 mM) with and without acid pre-treatment. Equivalence between the test (T) and reference (R) products was to be concluded if the 90% confidence interval for the T/R ratio for the capacity constant (k_2) was within 80 to 120%. This requirement is in line with the current FDA guidance document about sevelamer hydrochloride.

However, the phosphate concentration range chosen for the equilibrium study did not encompass the maximum binding of phosphate (as required by the current FDA Draft Guidance on sevelamer hydrochloride). The company has stated that this is because the study was designed against an older version of the FDA guidance document (August 2010). The TGA was concerned about the impact that this design flaw might have on the conclusion of equivalence between the proposed and innovator products.

To allay these concerns the company provided a bridging study which examined phosphate binding at maximum phosphate concentration levels (up to 70 mM; 2 replicates only). The k_2 values for the test and reference products in this study appear to be similar (and slightly higher than the values derived in the initial study), however 90% confidence intervals for the T/R ratios were not calculated. The significance of these results in demonstrating equivalence between the test and reference products remains unclear.

Advisory committee considerations

Details of this submission were presented at the 156th meeting of the TGA's Pharmaceutical Subcommittee (PSC) in May 2014. This was after the first round evaluation but before the sponsor's response to the TGA's consolidated request for further information was received. Based on the first round report the PSC advised that the differences between the proposed drug substance and the innovator's product (less titratable amines and increased cross-linking) suggest the proposed drug substance is therefore different from the proposed USP monograph. The PSC also agreed with the evaluator that there were concerns with the conduct of the phosphate binding study.

Recommendation No 2347

The PSC considered the submission by Generic Partners Pty Ltd to register Sevelamer GPPL, Sevelamer GXP, Sevelam, Sevlar, Apo-Sevelamer, Apotex-Sevelamer, Chemmart Sevelamer, Genrx Sevelamer and Terry White Chemists Sevelamer film coated tablets, containing 400 mg and 800 mg of sevelamer hydrochloride. This is a new generic medicine.

The Committee endorsed the questions raised by the TGA in relation to pharmaceutic and biopharmaceutic aspects of the submission.

The PSC concluded that the proposed submission is not acceptable on biopharmaceutic grounds. The biopharmaceutic characterisation of the drug product suggested differences with the innovator sufficient as to prevent its designation as a generic. In conjunction with the issues with phosphate binding due to the phosphate concentration range chosen for determining maximum phosphate binding capacity in the kinetic studies which failed to provide support for comparability.

The PSC advised that the absence of data to establish that the innovator product is identical to, or comparable with, the proposed generic product renders this submission unacceptable.

The PI should be amended to include statements on the following:

- *A statement on light protection is required as no photostability data are available.*
- *Many parts of the PI need to be corrected:*
  - *Under 'Description' remove spaces between numbers and percentage symbols.*
  - *Under 'Mechanism of Action', third paragraph, should read 4.46 (mmol/L)^2, i.e., use a superscript for the square notation.*
- *The Figure 2 caption should be locked with the figure on the same page.*
- *Page 4 of 13, '800' and 'mg' should be locked together on the same line.*
- *Page 7 of 13, 4.5' and 'g/kg/day' should be locked together on the same line.*
- *Page 8 of 13, for consistency, if 'in vitro' is in italics (preferred) then so should 'in vivo'.*
- *Page 12 of 13, lock '800' and 'mg' together on the same line, lock '8' and 'days' together on the same line.*

The PSC is of the view that the pKa should always be included in the chemistry section or product description whenever the pKa is of physiological relevance.

Quality summary and conclusions

The drug substance is a cross-linked polymer and the extent of cross-linking is very sensitive to the manufacturing conditions, which makes it difficult to match the relevant therapeutic properties of the drug substance between different manufacturers.

The level of total titratable amines in the drug substance is a surrogate assay parameter and also provides an indirect measure of its phosphate binding capacity. The most recently proposed titratable amine limit for the drug substance (and drug product) is 9.6 to 12.9 mmol/g. The proposed limit is looser that that specified in the draft USP drug substance monograph (11.3 to 14.1 mmol/g). This indicates that the proposed drug substance may have fewer free amine sites, compared with the innovator drug substance capable of functioning in an ion-exchange capacity. .[6]In the absence of an acceptable phosphate binding study and a clinical study using the proposed generic, the differences in

[6] The sponsor has since agreed to the draft USP specification (see *Response from sponsor* below).

the titrable amines in the drug substances in the proposed generic and innovator products may impact on the efficacy of the proposed generic product.

The swell index of the drug substance is proportional to the extent of cross-linking, which is inversely related to the free amine content. The free amine content is directly related to the drug substance phosphate binding capacity. Consequently, the swell index limit for the proposed drug substance should be aligned with the limit for the innovator product. The most recently proposed swell index limit for the drug substance is 6.9 to 9.4. The limit specified in the draft USP monograph is 6.2 to 8.4.[6]

Approval was not recommended for this submission as the drug substance in the proposed generic product is different to that in the innovator product and no bridging efficacy study has been performed to alleviate the concern regarding the impact of the difference in drug substances on the efficacy of the generic medicine.

III. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical Rationale

Chronic kidney disease is defined as either kidney damage or glomerular filtration rate (GFR) <60 mL/min/m^2 for ≥ 3 months. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) definitions of the stages of chronic kidney disease are presented in Table 1 below.

Table 1: Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73 m^2)
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderately decreased GFR	30 - 59
4	Severely decreased GFR	15 - 29
5	Kidney failure	<15 (or dialysis)

Apart from GFR, other renal functions that may be affected by chronic kidney disease include action as a filtration barrier to proteins, reabsorption or secretion of water or specific solutes and various endocrine functions. For example renal failure may cause parathyroid hormone excess and/or Vitamin D deficiency with resultant bone disease.

Sixty to 70% of intestinal phosphate is absorbed in the gut by two processes: passive diffusion across an electrochemical gradient between cells and via a transcellular sodium ion (Na+) dependent pathway via a co-transporter. Sixty to 70% of ingested phosphate is

absorbed in the duodenum and jejunum and 30 to 40% in the ileum. Serum phosphorus levels are higher in individuals with decreased renal function and there is evidence to suggest that serum phosphorus levels become abnormal in some patients at a GFR below approximately 60 mL/min/1.73 m^2.

Hyperphosphataemia is largely asymptomatic even at high levels. In patients with chronic kidney disease it tends to be chronic. Haemodialysis can remove phosphorus from the serum. Approximately 1000 mg of phosphorus can be removed per 4 h treatment with blood and dialysate flows of 300 mL/min and 500 mL/min respectively.[7] Most removal occurs early in dialysis.

Phosphate is a major mineral component of bone and excess phosphate alters bone pathology by several mechanisms. Phosphate complexes with serum calcium, leading to subnormal serum ionised calcium levels. The lowered calcium stimulates parathyroid hormone release (secondary hyperparathyroidism), as do high phosphate levels alone. Elevated parathyroid hormone levels result in high bone turnover, releasing calcium to normalise the calcium-phosphate imbalance.

High phosphate levels also inhibit renal alpha-1 hydroxylase which produces activated Vitamin D. Decreased activated Vitamin D reduces calcium absorption from the gut, decreased renal reabsorption of calcium and impaired bone mineralisation. This is manifest by bone pain and fractures.

Patients with kidney failure and uncontrolled hyperphosphataemia also develop extensive soft tissue calcifications including in the skin, joints and the eye.

Vascular calcification is a cause of significant morbidity and mortality as a consequence of chronic uncontrolled hyperphosphataemia. All types of blood vessels as well as the valves and conducting system of the heart can be involved.

Although dietary restrictions can be useful, additional measures may be required in patients with advanced kidney disease. Phosphate binders have been used to reduce serum phosphate. Phosphate binders containing calcium salts largely replaced aluminium containing products because of the toxicity from absorbed aluminium. However the calcium containing salts have the disadvantage of providing additional calcium and unwanted calcification from absorbed calcium.

Sevelamer hydrochloride is a phosphate binder that does not contain calcium.

Contents of the clinical dossier

Scope of the clinical dossier

No clinical trials using generic products for which this application pertains. The following documents were included with the submission:

- In vitro and kinetic studies.
- Published papers referenced in sponsor's Clinical Overview.

Paediatric data

The submission did not include paediatric data.

Good clinical practice

Not applicable. No clinical trials were conducted by the sponsor in support of this generic formulation.

[7] Daugirdas JT, Finn WF, Emmett M Chertow GM et al *The Phosphate Binder Equivalent Dose* Semin Dialysis 2011;24:41-48

Pharmacokinetics

Studies providing pharmacodynamic data

The sponsor has provided an in vitro equilibrium phosphate binding study and a kinetic phosphate binding study, and a justification for not conducting a bioequivalence study. The sponsor has only conducted the in vitro studies using the 800 mg dosage strength but has provided justification for studying only one dosage strength. The sponsor has not used an Australian brand product in in vitro equivalence studies and has provided a justification for so doing.

Evaluator's conclusions on pharmacokinetics

Sevelamer hydrochloride is a polymer that binds dietary phosphate in the gut. The reference product is not systemically absorbed and therefore bioequivalence studies are not suitable. The sponsor has chosen in vitro studies to establish equivalence between its generic product and the reference product Renagel. The studies are based on a draft FDA guidance document on in vitro studies for generic sevelamer hydrochloride compounds. The sponsor has used a non-Australian version of the reference product for its studies and has based its justification for so doing on Section 7 of Appendix 15 of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM). The sponsor has only conducted the FDA recommended studies on the 800 mg dosage strength, although there is a 400 mg strength of the reference product registered on the ARTG.

The reference product is a large polymer and each molecule forms a particle. The reference product has an average particle size range of 25 to 65 μm. Particle size is important for phosphate binding. The generic product does mention a lower limit for particle size raising the possibility of the presence of water soluble oligomers and monomers present in the formulation that may be systemically absorbed. It is therefore unknown if any systemic absorption would occur after taking this formulation and if so, what the implications for its safety and efficacy may be. From a clinical perspective, an absorption study could address the question of whether or not the generic formulation is absorbed in any potentially meaningful way. Also, the phosphate binding of the individual tablet may vary if there is insufficiently tight control on particle size with resultant differences in efficacy compared with the reference product. The issue of limits on the particle size has been identified by the TGA quality evaluator (see above).[8]

The reference product is a cross-linked polymer. The cross-linkages are important for phosphate binding and may have importance for the binding of off-target anions such as bicarbonate and low density lipoprotein cholesterol. The sponsor has described the conditions of manufacture at which it considers the generic product is sufficiently similarly cross-linked as compared to the reference product. The generic product is more cross-linked at 13.9 to 15.0% crosslinking as compared to the reference product's 10.6 to 13.9% cross-linking. The issue of the differences in cross-linking is under consideration by the quality evaluator.

Sevelamer swells in the presence of physiological fluids and the swelling is important for its phosphate binding. The reference product swells to 6 to 8 times its initial weight and 8 times its volume. The amount of swelling is related to the cross-linking within the molecule. The sponsor has not provided a measure of the swelling of the generic product but as the cross-linking of the generic formulation is different, the swell index is also likely to be different. The quality evaluator has identified this issue and additional information has been sought from the sponsor.

[8] The limits for particle size were subsequently resolved (see page 10 *Quality findings*).

Sevelamer hydrochloride 800 mg tablets are physically large. The reference product is approximately 19.04 mm x 9.76 mm x 7.6 mm. The final dimensions of the generic product after film coating have not been provided by the sponsor. The tablets have a larger mass than the reference products tested, although that may reflect a difference in the amount of excipient added to the active ingredient. There is concern regarding difficulty swallowing such a large tablet and whether it poses a choking hazard. The final physical dimensions of the generic 400 mg and 400 mg tablets have not been provided.

The sponsor has provided two vitro studies in support of the generic product. The first is an equilibrium binding study, conducted at 37°C. The characteristics of the phosphate binding are described using a Langmuir isotherm. The affinity constant of the reference product is 25% greater than that of the generic product and suggests a difference between the two products. The binding constants of the reference and generic products, however, are very similar.

The sponsor also conducted a kinetic in vitro study to show the phosphate binding of the generic and the reference product with time. Both products reached maximal binding within 15 minutes. The reference product has a phosphate binding capacity of 5.57 mmol/g ± 15%. The generic product had a mean phosphate binding capacity of approximately 98% of the reference product at free phosphate concentrations of 1 mM and pH 4.0 and 7.0. It had similar phosphate binding at free phosphate concentrations of 40 mM and pH 7.0 and approximately 94% at a pH of 4.0. The clinical significance of the difference at a 40mM concentration and pH 4.0 is unknown

The equilibrium and kinetic phosphate binding studies were conducted using the 800 mg dosage strength. The sponsor has provided a justification based on Section 4 of Appendix 15 of the ARGPM. There is qualitative proportionality of the active ingredients and excipients between the 400 mg and 800 mg dose forms. The portion of the guidance relating to the dissolution of the product is not relevant to sevelamer because it is insoluble in most solvents. Disintegration data is under evaluation by the quality evaluator. The sponsor has not addressed the issue of decreased efficacy if the effective dose is decreased.

It is not possible to demonstrate dose proportionality in terms of area under the plasma concentration versus time curve (AUC) for a given dose as sevelamer is not absorbed. Because there may be dose titration using the 400 mg dose if it is available and patients may elect to take two 400 mg tablets instead of one 800 mg tablet because of ease of swallowing, the dose-response relationship with increasing dose is of clinical importance. Because the results from the study by Burke et al 2007[9] did not demonstrate this type of proportional dose-response between the 1g three times daily (tds) and 2.5g tds dosages for urinary and faecal phosphate or LDL cholesterol it is unclear whether two 400 mg tablets would provide the same phosphate binding as one 800 mg tablet and a comment from the sponsor has been requested.

Disintegration testing is a requirement of the FDA guidance. It is not known if there would be any clinical implications from the slower disintegration time for the generic formulation, as sevelamer hydrochloride should be taken with meals and is likely to remain in an acid environment for a minimum of 20 to 30 minutes.

The sponsor has chosen to use overseas reference products in preference to Australian reference products and has relied on the guidance from Section 7 of Appendix 15 of the ARTG. The guidance generally refers to products with have measurable pharmacokinetics. The quality evaluator has evaluated the information provided by the sponsor in support of the use of the overseas product.

[9] Burke SK, Slatopolsky EA and Goldberg, DI; Nephrol Dial Transplant (1997) 12: 1640–1644.

Pharmacodynamics

Studies providing pharmacodynamic data

The sponsor has not provided any pharmacodynamic data for the generic formulation of sevelamer hydrochloride. The sponsor states that on the basis of the presented in vitro studies the generic formulation and the reference product are of sufficient physicochemical similarity that the pharmacodynamic effects of the reference product can be extrapolated to the generic formulation.

Evaluator's conclusions on pharmacodynamics

The sponsor has not conducted pharmacodynamic studies using the generic formulation.

Sevelamer hydrochloride exerts its pharmacological effects as an ion-exchange resin in the gut. It is non-selective and while the target anions are phosphate, off-target anions include some with clinical consequences such as interaction with some medications, bicarbonate, bile acids with an associated decrease in levels of fat soluble vitamins including Vitamin D, levothroxine, mycophenolate mofetil, uric acid, vitamin C and folate. Other negatively charged medications that undergo enterohepatic circulation are potential substrates for binding with sevelamer.

The quality evaluator has raised concerns that the generic and reference products may not be chemically the same, both structurally and in terms of phosphate binding. Of particular interest is whether the geometry of the molecule, its cross-linking and the particle size result in the binding of other anions to a lesser or greater extent as this may have clinical consequences. This is important clinically as the prescriber will generally not know if the patient has been dispensed the reference product or a generic product by their pharmacist.

Dosage selection for the pivotal studies

No clinical trials were provided in this application.

Efficacy

Studies providing efficacy data

The sponsor has not provided any studies investigating the clinical efficacy of the generic formulation.

Evaluator's conclusions on efficacy

The sponsor has not provided any data on the clinical efficacy of the generic formulation.

The clinical overview and the references provided support the use of sevelamer hydrochloride as a therapeutic option to decrease serum phosphate, reduce the calcium phosphorus product and reduce iPTH[10]. Improvements in these parameters have implications for bone health and cardiovascular disease.

The basic premise of the sponsor's submission is that only in vitro studies are required in support of the registration of the generic formulation. This additional information describing the efficacy of the reference product, although helpful, does not of itself

[10] A measurement of parathyroid hormone (PTH) is the intact PTH (iPTH) assay.

demonstrate the therapeutic equivalence of the reference and generic formulations. As there are outstanding concerns regarding the similarity of the physicochemical properties of the generic formulation as compared with the reference product, there is insufficient surety of the therapeutic equivalence of the generic formulation and the reference products. This uncertainty may be overcome with a clinical trial comparing the two formulations.

Safety

Studies providing safety data

The sponsor has not provided any studies evaluating the clinical safety of the generic formulation.

Evaluator's conclusions on safety

The sponsor has not provided any evidence for the clinical safety of the generic formulation.

As mentioned previously, there is at this time some uncertainty regarding the therapeutic equivalence between the reference and generic formulations, including the safety profile.

As the sponsor has not indicated a lower limit for the particle size concern is raised regarding the presence of allyl amine monomers and small oligomers that may be absorbed. The clinical safety implications of a measurable systemic absorption of a portion of this formulation are unknown but at this time there is no certainty that it is negligible.

The size of the 800 mg tablet is a concern. The final physical dimensions of the tablet have not been provided. Difficulty swallowing tablets occurs at all ages. Factors affecting swallowing include increasing age due to age related changes in salivary gland, oropharyngeal and/or oesophageal muscle function; certain co-morbidities such as with scleroderma or after stroke and with some medications such as those with anticholinergic effects. Although it is recognised that the issue of large tablet size and potential choking hazard is present in the reference product and that there are warnings already in place in the PI, the generic product should not exceed the dimensions of the reference product for these reasons. A large tablet size is also a tolerability concern in that patients who have difficulty swallowing tablets and more likely to miss doses or be completely non-compliant with the therapy. Failure to comply with therapy is associated with possible increased morbidity and mortality. There is no clinical information in the submission that addresses the issue of whether swallowing difficulties and the potential choking hazard is are equal to or less than those recognised for the reference product.

The swell characteristics of the final product have not been provided. The reference swells to 6 to 8 times its original weight and 8 times its volume. This of itself raises safety concerns around the potential for gastrointestinal tract obstruction including intestinal obstruction and partial obstruction of the oesophagus, especially in patients with ulceration and strictures, and for adverse outcomes if the tablet is lodged outside the gastrointestinal tract. The sponsor has not provided evidence that the generic product does not swell more than the reference product.

Metabolic acidosis is a safety concern. It is expected that HCl would be liberated from the generic product on binding of phosphate ions as it is with the reference product. It is unknown whether binding of bicarbonate ions in the gut occurs similarly between the reference and generic products.

With the outstanding concerns regarding the physicochemical similarity between the reference and the generic formulation as yet unresolved, the safety profile characterised for the reference product cannot be extrapolated to the generic product with confidence.

Trade names

Two of the proposed trade names give cause for concern with regards to look alike and sound alike medication errors. The proposed trade name Sevelam looks like Sevelon, particularly when handwritten, sounds alike when the emphasis is placed on the first syllable and is therefore unacceptable. Furthermore, the proposed trade name Sevlar both sounds and looks like Sevikar and is unacceptable.

First round benefit-risk assessment

First round assessment of benefits

The benefits of the generic formulation of sevelamer hydrochloride in the proposed usage are:

- The presence of an alternative product in the market in the event of a shortage of the reference product.
- Offers a choice to the consumer.
- As the 400 mg tablet is not marketed by the sponsor of the reference product, a 400 mg product would offer the prescriber options for dose titration. The 400 mg tablet is likely to be smaller than the 800 mg tablet and would be easier to swallow. The sponsor has indicated in the Consumer Medicine Information (CMI) that this dosage strength will not be marketed. If this is the case, the potential benefits of this dosage strength would not be realised.

The physicochemical properties of the generic formulation have not yet been established as sufficiently similar to the reference to accept bioequivalence based on the outcome of the in vitro studies as presented. It is not possible to extrapolate of the known benefits of the reference formulation of sevelamer hydrochloride to the generic formulation with any certainty at this time.

First round assessment of risks

The risks of the generic formulation in the proposed usage are:

- No human data for the generic product to establish that its pharmacodynamic, efficacy and safety characteristics are the same as the reference product
- No lower limit on particle size and no evidence there are no water soluble monomers or oligomers that could be absorbed and no studies that show there is not absorption in human. The pharmaceutical or toxic actions, if any, of absorbed monomers are unknown. Particle size is also important for efficacy. No in vivo studies have been performed. Efficacy and pharmacodynamic effects of the reference product have not been investigated in human subjects and are unknown for the generic product.
- There is a higher percentage of cross-linking in the generic formulation compared with the reference product, with the potential for increased swelling as the two properties are related. Cross-linking that differs from the reference product may result in a different capacity to bind dietary phosphate but also may affect drug-drug interactions and interactions with other anions, including bile salts. Swelling has safety

implications with the potential to cause bowel obstruction, oesophageal obstruction, and airway obstruction if the tablet is inadvertently inhaled.

- The proposed tablet size is large. The final dimensions are not provided but the press size for the uncoated 800 mg tablet is 19.00 mm x 9.5 mm x 8 mm. This may pose a choking hazard, particularly in the target population who are often elderly with significant co-morbidities.
- Other safety concerns of relevance to the reference product may be of relevance to the generic product, such as metabolic acidosis and the potential for intestinal obstruction and vitamin deficiencies. Whether these occur with a similar frequency and with a similar severity compared to the reference product is unknown and cannot be assumed with certainty.

First round assessment of benefit-risk balance

The sponsor has not provided any clinical data from the use of the generic product in this submission but has relied on two in vitro studies to demonstrate bioequivalence of the generic and reference products.

The sponsor has relied on FDA guidance to support its approach to this submission for registration of a generic product. However, the reliance is on a method for establishing bioequivalence for sevelamer hydrochloride. The justification for undertaking these studies alone is contingent upon demonstration of the chemical equivalence of the two formulations. There are concerns raised by the quality evaluator regarding the equivalence of physicochemical properties of the generic product compared with the reference products. Of specific concern are the potential differences in particle size, cross linking and phosphate binding characteristics of the generic product as compared with the reference product. Additional data and clarification will be sought from the sponsor by the quality evaluator.

The concern regarding the particle size is relevant for the efficacy of the product. There is evidence in the submission that particle size is related to phosphate binding in a nonclinical study and controlling the particle to size to be within the same range as that of the reference product would appear to be important for its clinical efficacy of phosphate binding. There is no human data to suggest there are no differences in efficacy between the generic and reference products in the target population. There is currently no lower limit to the particle size, suggesting there may be monomers or small oligomers that may be absorbed. The clinical consequences of this are unknown.

Cross-linking is important for the geometry of the molecule, its ion binding and its swelling. There is a difference in cross-linking between the generic and reference products. No data has been provided that the generic product swells in the same proportions as the reference product. There are potential safety concerns regarding the swelling of the product particularly if it lodges outside the gastrointestinal tract but also if it draws more fluid from the gut contents than the reference product and is associated with a greater risk of constipation and therefore bowel obstruction.

The binding of other anions has not been tested and there is concern regarding the physicochemical properties of the generic product compared with the reference product. In the absence of clinical data to suggest otherwise, there is concern regarding potential differences in the binding of other anions.

The final dimensions of the tablets of the generic product have not been provided. The sizes of the compression moulds of the generic tablets have been provided and the assumption must be made that film coating will add to the size of the tablet. Swallowing difficulties are recognised by the sponsor of the reference product and warnings appear in the PI and CMI for Renagel. This is of great concern as the reference product is

approximately 19mm in maximum dimension and further increases in size will have implications for the safety (potential choking hazard) and tolerability (poor compliance when tablets are difficult to swallow). This concern is increased as the potential for the swelling of the tablet is not quantified.

The proposed indication is for the reduction of serum phosphate in patients with Stage 4 or 5 chronic kidney disease. The target population has end stage renal disease (ESRD). This is a complex metabolic disorder and multiple therapeutic interventions are required in patient management. It is important that any generic medication not only binds dietary phosphate in the same manner and to the same degree as the reference product but that it has the same interaction with other medications and other ions in order that patients and clinicians can be confident of the interchangeability of the generic and reference products. The behaviour of the polymer in vivo has not been tested in any model.

The potential benefits of an alternative sevelamer hydrochloride product in the market place in terms offering a choice of a 400 mg dosage form with a smaller, potentially easier to swallow tablet and the potential benefits of choice for patients and alternatives in the event of a shortage of the reference product, are outweighed by the concerns outlined above. There are no clinical data to characterise the safety and efficacy of the generic product compared with the reference product and that comparability cannot be assumed.

The benefit-risk balance of the generic formulation of sevelamer hydrochloride, given the proposed usage, is unfavourable.

First round recommendation regarding authorisation

It is recommended that the submission as it stands is rejected. The reasons for this recommendation are as follows:

- The lack of specification of particle size in the generic formulation and the lack of mention of a specific lower limit for particle size. There is nonclinical data to show that particle size is important for the therapeutic effect. It is possible that monomers and oligomers within the formulation may be systemically absorbed. The safety outcomes related to these molecules is unknown. There are no clinical data in support of the safety and efficacy of the generic product and to indicate that the concerns regarding particle size are of no clinical consequence.
- The difference in cross-linkages in the molecules between the reference and the generic formulations. Cross linkages within the molecule are important for arrangement of binding sites for phosphate. There is an absence of evidence to suggest a difference in molecular geometry is of no clinical consequence. The binding of other anions including bile acids, other drugs and bicarbonate is important for the interchangeability of the generic and reference products. Crosslinking is also related to the swelling of the molecule.
- There is missing information regarding the final size of the tablet. A possible increased difficulty swallowing the tablet if the final dimensions are larger than the reference product cannot be ruled out in the absence of this information.
- The sponsor has not provided clinical data to suggest that the differences in chemical properties between the generic and reference product are of no clinical consequence. The efficacy, safety and tolerability of the generic as compared with the reference product are unknown.

Clinical questions

Pharmacokinetics

1. The sponsor submitted a justification for the use of in vitro studies alone to determine similarity between the generic formulation of sevelamer hydrochloride and the reference product. However, there have been issues raised including possible differences of particle size and particle size distribution, cross-linkages within the molecule and tablet size between the generic and reference formulations. Given these issues, the sponsor is requested to address the following questions below:

    a. A potential difference between the reference formulation and the generic formulation is the particle size and control for monomers and small oligomers. As there is no description of a control on the lower limit of the particle size and no absorption study in the submission to demonstrate that the generic formulation is not systemically absorbed, then please discuss the basis for the conclusion that there is no systemic absorption of the generic formulation and that it only acts locally within the gastrointestinal tract.

    b. Please indicate upon what basis the pharmacodynamic interactions (drugs and other molecules such as bile salts) described for the reference can be assumed for the generic formulation, given the potential difference in particle size distribution and cross-linkages between the reference formulation and the generic formulation.

    c. In reference to the justification for not including a bioequivalence study the sponsor states that the clinical risk from any 'slight bioinequivalence' is low based on short term data derived from healthy volunteers. Please define 'slight bioinequivalence'. Please discuss the clinical consequences of this 'bioinequivalence' for the target population, which often has significant co-morbidities and who may take this product over the long term. In this discussion please include a discussion of the clinical efficacy, safety and tolerability of the reference and the generic products.

2. A justification is provided for not performing in vitro studies using the 400 mg strength tablet. In this justification, the dose proportionality of ingested tablets between 800 mg tablet and 400 mg tablets is assumed on the basis of their derivation from a common blend of ingredients. However, in Burke et al 1997[9] a dose of 2.5g of sevelamer 500 mg capsules did not bind double the phosphate of a 1.25 g dose, which suggests that there is not a direct linear relationship between phosphate binding and dose. Please discuss the clinical implications of this observation for the generic formulation as patients may choose to take two 400 mg tablets in preference to one 800 mg tablet and to support the registration of a 400 mg strength tablet.

Safety

3. The reference product carries a warning about choking for its tablet. The sponsor states that the generic 800 mg tablet is pressed into a 19 x 9.5 mm plain mould. Please provide the final physical dimensions of the generic product compared to the Australian reference product and if there are differences in size, shape or swell volume then discuss the clinical consequences for patients, including the potential for choking, and the risks of swelling and tablet size if the tablet is lodged in the airway or in the upper gastrointestinal tract.

Other questions

4. An application for approval for this generic formulation was made in the EU (Germany) in December 2012. Please provide an update on the status of that application. In your response please include information about the following:

a. whether additional data or other information has been requested of the applicant in support of the application in Europe; and/or

b. whether there has been a requirement to undertake any further in vitro studies, animal studies or human clinical trials to support the application.

Where additional information has been requested please provide the questions asked and the responses the sponsor provided. If additional studies have been requested please provide details of the request and a synopsis of the studies the sponsor is planning to conduct.

Second round evaluation of clinical data submitted in response to questions

For details of the sponsor's responses to the Clinical questions and the clinical evaluator's comments on these responses please see Attachment 2.

Second round benefit-risk assessment

Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of the generic version of sevelamer hydrochloride in the proposed usage are unchanged from those identified in the First Round Evaluation.

Second round assessment of risks

After consideration of the responses to clinical questions, the risks of the generic version of sevelamer hydrochloride in the proposed usage are unchanged except for the following:

- The mean final dimensions are 19.0431 mm x 9.534 mm x 8.328 mm. This may pose a choking hazard, particularly in the target population who are often elderly, with significant co-morbidities. Poor compliance or non-compliance may result from difficulty swallowing the tablet. Although the reference product is very large, the generic product is larger in length and thickness. Using the mean physical dimensions of the generic and reference products provided by the sponsor, the volume of the generic product is greater than the reference product (approximately 791.6 mm^3 and 736.38 mm^3 respectively)[11] and the cross-sectional area of the generic is also larger than the reference product (approximately 62.36mm^2 and 58.28mm^2, respectively)[12]. There is no clinical data to assess the safety and tolerability of the generic product. Whether it is more difficult to swallow and poses a greater choking risk than the reference product is unknown. The sponsor has suggested that it would be willing to consider additional warnings in the PI and CMI regarding this risk, although it is not clear whether this would be sufficient to mitigate any increased risk.
- The sponsor has provided additional information regarding the swelling of the product. In the specification provided, the sponsor has indicated the swell index specification is set to 6.0 to 10.0. This is greater than that reported by Plone et al 2002[13] for the reference product. The quality evaluator will comment further on this but from a clinical perspective the concern is that the generic product may have an increased risk of constipation and intestinal obstruction if its swell index is greater than the reference product. If a generic tablet lodged in the airway there is the

[11] Approximating volume of an ellipsoid figure $V = {}^4/_3\pi\, r^1\, r^2\, r^3$

[12] Approximating cross-sectional area of an ellipse $A = \pi\, r^1\, r^2$

[13] Plone MA, Petersen JS, Rosenbaum DP and Burke SK; Clin Pharmacokinet 2002; 41 (7): 517-523

potential for a larger obstruction to occur, due to the swelling, than with the reference product.

- The sponsor has addressed the issue of the control of the particle size such that monomers and water soluble oligomers are unlikely to be present in the formulation in that the lower limit of the particle size will be controlled and the impurity limit of water soluble oligomers will be no more than 0.2%.

Second round assessment of benefit-risk balance

The sponsor has chosen in vitro studies to demonstrate the phosphate binding of the generic formulation compared with the reference product. The sponsor has demonstrated that under the conditions of the in vitro studies the generic product binds phosphate ions. The characteristics of the binding differ between the generic and reference products for the affinity constant (k1) of the Langmuir equation, although the binding constants are similar. The kinetic binding study showed both the reference and generic products bind phosphate ions within 15 minutes but because the time points between 0 and 15 minutes have not been measured any difference between the generic and reference products is unknown. The sponsor has also provided evidence that the dose-response relationship for the reference product is complex. This raises uncertainty as to whether the clinical activity of the generic product is adequately characterised by in vitro studies alone.

The sponsor has addressed the issue of the lower limit of the particle size. The particle size distribution is still of concern although the sponsor has provided a justification for not comparing its product to the reference product. The adequacy of this justification will be assessed by the quality evaluator. Particle size is important for phosphate binding but also be important for the binding of other anions.

The sponsor has provided a justification for not performing the phosphate binding studies on the 400 mg product. Although there is quantitative proportionality between the 400 mg and 800 mg doses, the sponsor has provided evidence that the dose-response curve in terms of serum phosphate bound in the target population is flat, suggesting the assumption that the 400 mg tablet should bind half the phosphate of the 800 mg tablet or that two 400 mg tablets should be interchangeable with one 800 mg tablet may not be valid in the patients with renal disease.

The sponsor has further clarified its justification for assuming that the difference in cross-linking is unlikely to be of any clinical consequence but there is no clinical data to support the assumption and its validity is untested. Although, as the sponsor states there is an overlap in the percentage of cross-linking between the polymers the percentage of cross-linking at the upper end of the range of crosslinking for the reference product and the lower end of the generic product. The cross-linking for most polymer molecules is likely to differ between the generic and reference products for the majority of polymer molecules manufactures and as previously discussed, may be of clinical relevance. Cross-linking is also related to the amount the product swells. The reference product has been associated with constipation and bowel obstruction. Additional swelling adds to the safety concern, particularly for patients with renal failure with an increased risk of slow colonic transit time.

There is acknowledgement by the sponsor that the 800 mg tablet size is large and swallowing difficulties may be encountered and it may be a choking hazard. The tablet must be swallowed whole and the sponsor proposes to add labels to the packaging to remind patients of this. Whether the generic formulation is more difficult to swallow is untested. If so, it is unclear whether additional warnings in the PI and CMI would be sufficient to mitigate the risk.

The benefit-risk balance of this generic version of sevelamer hydrochloride, given the proposed usage, is unfavourable.

Second round recommendation regarding authorisation

Following review of the sponsor's responses to the Clinical questions, the recommendation is for rejection of the application on the following grounds:

- There are physicochemical differences between the generic and reference products which include a difference in the affinity constant for the Langmuir isotherm at 37^{o}C, a difference in cross-linking and the swell index. These relevance of these differences in chemistry have not been
- Therapeutic equivalence between the generic and reference products has not been tested in humans and it is unclear whether the generic and reference products are of sufficiently similar safety and efficacy such that they can be used interchangeably as could be the case if the generic formulation is approved.
- There are the differences in chemistry between the reference and generic products which raises the possibility of differences in safety and efficacy in patients with ESRD. The validity of the concerns regarding these potential differences is unknown because of the lack of clinical data. The target population has Stage 4 or 5 ESRD and requires therapy to reduce serum phosphate. This is a complex disorder in patients that are often elderly, with significant co-morbidities and on multiple medications. This lack of clinical information regarding differences in safety and efficacy of the generic product and the reference product poses an unacceptable risk for these patients.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a European Union Risk Management Plan (EU-RMP) Version: 1.0 (September 2012) with an Australian Specific Annex (ASA) Version 1.0 (September 2013) which was reviewed by the TGA's Post-Marketing Surveillance Branch (PSMB).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 2.

Table 2: Sponsor's summary of the Ongoing Safety Concerns

Safety concerns	
Important identified risk	Vitamin deficiency
	Peritonitis
	Worsening of metabolic acidosis
Important potential risks	Intestinal Obstruction/ileus
	Increased thyroid stimulating hormone levels/Hypothyroidism
	Hyperphosphataemic CKD patients on peritoneal dialysis
	AV fistula site adverse reactions

Safety concerns	
	Increased sodium chloride levels
	Drug interactions
Important missing information	Paediatric patients
	Pregnancy and Lactation
	Hyperphosphataemic CKD patients not on dialysis with serum phosphorus > 1.78 mmol/l
	Patients with hepatic insufficiency

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance activities to monitor all specified safety concerns.

Risk minimisation activities

Routine risk minimisation activities are proposed for all safety concerns. The sponsor provides the Australian epidemiological information on the population to be treated in the ASA.

Reconciliation of issues outlined in the RMP report

Table 3 summarises the RMP's first round evaluation of the RMP, the sponsor's responses to issues raised by the RMP evaluator and the evaluation of the sponsor's responses.'

Table 3: Reconciliation of issues outlined in the RMP report

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
1. Safety considerations may be raised by the clinical evaluators through the TGA's consolidated request for further information and/or the Clinical Evaluation Report. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.	The sponsor does not appear to make any direct response to this recommendation.	In the light of the clinical evaluator's comments (see above) the sponsor should include the important potential risk: 'Swallowing difficulties and the potential for lodgement in the airway or upper gastrointestinal tract' as an ongoing safety concern and give consideration to appropriate pharmacovigilance and risk minimisation activities. Such revision should be reflected in an amended ASA before this application is approved.

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
2. It is recommended that the following be added to the list of potential safety concerns: 'Potential Off-label use'.	The sponsor has replaced the important missing information: 'Paediatric patients' with 'Potential off-label use, including paediatric patients' to be monitored by routine pharmacovigilance activities with routine risk minimisation applied.	This is acceptable.
3. The safety and efficacy of this product has not been established in patients below the age of 18 years and this is mentioned in the PI. However, there has been significant off-label use of sevelamer in paediatric patients in USA. The Delegate may wish to update the Australian PI to strengthen the wording (that is, '*Sevelamer is not recommended in children below the age of 18 years*') in order to discourage the use of sevelamer in paediatric patients.	The sponsor does not appear to make any direct response to this recommendation to the Delegate.	This recommendation to the Delegate regarding revision to the PI is still open for consideration.[14]
4. The Delegate may wish to update the Australian PI to strengthen the wording in order to discourage the use of sevelamer in pre-dialysis patients.	The sponsor does not appear to make any direct response to this recommendation to the Delegate.	This recommendation to the Delegate regarding revision to the PI is still open for consideration.[15]
5. The sponsor states in Section 1.5.2 on the RMP '*In patients undergoing peritoneal dialysis additional monitoring of fat-soluble vitamins and folic acid is recommended'.* The sponsor also states in Section 4 *'In preclinical studies in rats and dogs, sevelamer hydrochloride at a dose of 10 times the maximum human doses reduced absorption of fat soluble vitamins D, E and K, and*	The sponsor does not appear to make any direct response to this recommendation to the Delegate.	This recommendation to the Delegate regarding revision to the PI is still open for consideration.[16]

[14] At Milestone 5 the sponsor provided the following response: '*The sponsor has no objection to including the recommended text "Sevelamer is not recommended in children below the age of 18 years" and is willing to incorporate text amendments in accordance with the corresponding change for the innovator Renagel PI'*.

[15] At Milestone 5 the sponsor provided the following response: '*The sponsor has no objection to revising the text in the PI in relation to pre-dialysis patients and is willing to incorporate text amendments in accordance with the corresponding change for the innovator Renagel PI.'*

[16] At Milestone 5 the sponsor provided the following response: *'The sponsor has no objection to revising the text in the PI in relation to monitoring folic acid levels and is willing to incorporate recommended text amendments in accordance with the corresponding change for the innovator Renagel PI.*'

Recommendation in RMP evaluation report	Sponsor's response	RMP evaluator's comment
folic acid'. The reduction in folic acid level is also mentioned in Summary of Product Characteristics (SmPC). SmPC states that *'There is at present insufficient data to exclude the possibility of folate deficiency during long term Sevelamer Hydrochloride treatment'* under section 4.4 'Special warning and precautions for use'. However, in the Australian PI there is no recommendation made to monitor folic acid level in patients undergoing peritoneal dialysis and during long term Sevelamer Hydrochloride treatment. The Delegate may wish to revise the Australian PI to address the additional monitoring of folic acid in patients undergoing peritoneal dialysis and during long term Sevelamer Hydrochloride treatment.		

Summary of recommendations

It is considered that the sponsor's response to the TGA has not adequately addressed all of the issues identified in the RMP evaluation report.

Outstanding issues

Issues in relation to the RMP

The sponsor was asked to respond to safety considerations raised by the clinical evaluator through the TGA's consolidated request for further information and/or the Clinical Evaluation Report in the context of relevance to the RMP. The sponsor does not appear to make any direct response to this recommendation. Nevertheless in the light of the clinical evaluator's comments the sponsor should include the important potential risk: 'Swallowing difficulties and the potential for lodgement in the airway or upper gastrointestinal tract' as an ongoing safety concern and give consideration to appropriate pharmacovigilance and risk minimisation activities. Such revision should be reflected in an amended ASA before this application is approved.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

ACSOM advice was not sought for this submission.

Suggested wording for conditions of registration

RMP

1. The European Risk Management Plan (Version: 1.0 dated September 2012) with an Australian Specific Annex (Version: 2.0, dated 25 March 2014) to be revised to the satisfaction of the TGA, must be implemented.

Key changes to the updated ASA

In their response to the TGA, the sponsor provided an updated ASA (Version: 2.0, dated 25 March 2014). Key changes from the version evaluated at First Round Evaluation are summarised below in Table 4.

Table 4: Key changes to the ASA

	Key changes
Ongoing safety concerns	The important missing information: 'Paediatric patients' has been replaced by 'Potential off-label use, including paediatric patients' to be monitored by routine pharmacovigilance activities with routine risk minimisation applied.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Given that sevelamer acts locally in the intestinal tract and is not systemically absorbed, no bioequivalence studies were performed to compare this generic with Renagel, as is normally the case for an oral preparation such as a tablet. The sponsor has also not conducted any clinical studies with this generic product to assess its efficacy and safety, that is, no patients have been given this generic product. The submission therefore relies on the chemistry data submitted along with two in vitro binding studies to ascertain if this product is a generic of Renagel.

When the submission was initially lodged by the sponsor, the TGA raised concerns as follows:

a. The extent to which serum phosphate is affected by the actions of this polymer, which cannot be established using in vitro data. It was suggested that clinical data is obtained from patients within the target population.

b. The molecular weight distribution is not well defined and may have safety and efficacy implications, which could be properly addressed in a clinical trial.

c. The dimensions of the final tablet size are not provided but the mass is substantially increased in the proposed tablet.

d. The in vitro studies, whilst supportive, cannot replace studies in the target population with pharmacodynamic endpoints, which would also provide important safety and tolerability data.

Following the second round evaluation phase, both the quality evaluator and the clinical evaluator could not recommend approval. The quality evaluator also sought the advice of PSC at its meeting on 26 May 2014, following the first round of evaluation, on whether this product could be considered a generic of Renagel and whether the sponsor had demonstrated that the phosphate binding capacity of this generic was equivalent to Renagel. The PSC advised at Recommendation 2347 that the proposed submission was not considered acceptable on biopharmaceutic grounds, the characterisation of the drug product suggested differences with Renagel and the phosphate concentration range chosen for determining maximum phosphate binding capacity in the kinetic studies, which failed to provide support for comparability. The full PSC Recommendation is included under Quality findings above.

Following the PSC advice, the sponsor submitted additional data comparing their generic product with the reference product to address concerns of cross-linking, level of titratable amines and phosphate binding capacity. Evaluation of this data by the quality evaluator concluded that approval was not recommended due to the proposed drug product containing a slightly lower level of titratable amines than the reference product and that this reflected differences between the phosphate binding capacity of the proposed drug product as compared with the reference product. The evaluator concluded that the only way to ensure equivalence between the proposed and reference products was if their respective drug substance and drug product specifications were matched. There was also concern regarding the upper particle size limit which needed to be tightened to control tablet swelling upon ingestion. It was also recommended that the sponsor repeat the phosphate binding capacity study as it did not encompass the maximum binding of phosphate as required by the draft FDA guidance document for sevelamer, which raised doubts about the validity of the results showing equivalent phosphate binding between the generic and reference products.

A meeting was held between the TGA and sponsor on 20 June 2014 to discuss the concerns of the TGA including the lack of clinical data to demonstrate equivalence between this generic and Renagel, the limit for titratable amines, the limits for phosphate binding, whether a bicarbonate binding study was needed (a reduction in bicarbonate has been reported with sevelamer), the need to repeat the phosphate binding test in line with current FDA guidance, the swell index should be aligned with the USP monograph, the concern with the size of the tablet (video footage comparing the generic with Renagel would be provided), the lack of particle size limit results and whether a small swallowing study should be conducted.

In response to the above meeting, the sponsor submitted further information to the TGA. The quality evaluator concluded that the proposed limits of the particle size distribution were now acceptable, a tighter limit was proposed by the sponsor for the total titratable amines but this was still looser than that specified in the USP monograph. The sponsor was willing to tighten the phosphate binding capacity limits in the drug substance and drug product and to tighten the limits for the swell index.

The sponsor also responded to the clinical concerns regarding tablet size, disintegration and whether there was a need for a bicarbonate study, however the clinical evaluator's recommendation in the clinical evaluation report remained unchanged. This was mainly due to a lack of clinical data and concern with the tablet size. The sponsor did not repeat the phosphate binding study according to the current FDA guidance. The main concern with the original study was that it did not include a phosphate concentration that induced maximum binding of phosphate with the drug substance. The sponsor did provide results from a bridging study that examined phosphate binding at maximum phosphate concentration levels. This showed similarity between the generic and reference product for the capacity constant but it was limited by its design of only including two replicates tests and did not include 90% confidence intervals. The response also indicated that in Germany where the same submission has been lodged, several issues were raised regarding the quality of the drug substance and product however no questions were asked regarding the equivalence of the generic and reference products with regard to phosphate binding capacities. The quality evaluator again advised that approval was not recommended due to uncertainty on the equivalence of the generic and reference in terms of total titratable amines and the swell index. The proposed limits for these substances were not commensurate with the USP monograph. The significance of these differences was unclear in the absence of a phosphate binding study conducted in accordance with the current FDA guidelines.

This sevelamer generic product has not been previously considered by the TGA's Advisory Committee on Prescription Medicines (ACPM) and there are no other generic products of sevelamer registered on the ARTG.

This sevelamer generic product has not been approved overseas. An application was submitted to Germany in December 2012 and was under evaluation at the time of writing.

Quality

The quality evaluator has recommended rejection of the submission due to '*the drug substance in the proposed generic product is different to that in the innovator product, and no bridging efficacy study has been performed to alleviate the concern regarding the impact of the difference in drug substances on the efficacy of the generic medicine*.'

Sevelamer hydrochloride and sevelamer hydrochloride tablets are not subject to BP or USP monographs; however draft USP monographs are available for both the drug substance and drug product. Due to the complexity and nature of the drug substance, the quality control tests and limits applied to the drug substance play an important role in establishing that the drug substance in the proposed generic product is the same as that in the innovator product. The limits proposed for some quality control tests for the drug substance in the proposed generic product are different to those in the draft USP monograph The drug substance is a cross-linked polymer and the extent of cross-linking is very sensitive to the manufacturing conditions, which makes it difficult to match the relevant therapeutic properties of the drug substance between different manufacturers.

In assessing the quality control of the drug substance, there are key tests and limits applied. These include: identification; phosphate binding capacity; chloride content; swell index; total titratable amines; water soluble oligomers; allylamine content; epichlorohydrin content and particle size. The evaluator has advised that the limits and tests for identification, chloride content, water soluble oligomers, allylamine content, epichlorohydrin content and particle size are in line or tighter than those specified in the draft USP monograph for sevelamer hydrochloride and all tests have been adequately described and validated. The issues of concern relate to the phosphate binding capacity of sevelamer, the swell index (indirectly inversely related to free amine content and therefore phosphate binding capacity) and total titratable amines (surrogate measure of phosphate binding capacity).

The level of total titratable amines in the drug substance is a surrogate assay parameter and also provides an indirect measure of its phosphate binding capacity. The most recently proposed titratable amine limit for the drug substance (and drug product) is 9.6 to 12.9 mmol/g. The proposed limit is lower than that specified in the draft USP drug substance monograph (11.3 to 14.1 mmol/g). The level of titratable amines is directly linked to the phosphate binding ability of the drug substance and drug product. This indicates that the proposed drug substance may have fewer free amine sites, compared with the reference drug substance capable of functioning in an ion-exchange capacity.

To address the concerns and recommendation for rejection by PSC, the sponsor provided a comparison of total titratable amines and phosphate binding capacity of the generic and Renagel as noted in *Quality findings* above. The data implies that the proposed generic drug substance has fewer free amine sites as compared with the reference drug substance capable of functioning as a phosphate binder.

The apparent difference in titratable amines between the generic and Renagel is reflected in differences between the phosphate binding capacities of the two drug substances.. Although the differences appear marginal, these may impact on the efficacy of the proposed generic product.

In the absence of an acceptable phosphate binding study or a clinical study using the proposed generic, the differences in the titratable amines in the drug substances in the generic and reference products may impact on the efficacy of the proposed generic product.

The swell index of the drug substance is proportional to the extent of cross-linking, which is inversely related to the free amine content. The free amine content is directly related to the drug substance phosphate binding capacity. Consequently, the swell index limit for the proposed drug substance should be aligned with the limit for the reference product. The most recently proposed swell index limit for the drug substance is 6.9 to 9.4. The limit specified in the draft USP monograph is 6.2 to 8.4.

Since a bioequivalence study could not be performed for this product, the sponsor submitted two in vitro studies: an in vitro equilibrium binding study and an in vitro kinetic binding study as per a draft FDA guidance on sevelamer hydrochloride dated August 2010 [the current version from August 2011 has updated testing requirements]. The sponsor conducted these studies using the 800 mg strength but used the European Renagel as a reference which was deemed acceptable by the TGA in this instance.

For the equilibrium binding study, which is considered the pivotal in vitro study, the sponsor compared the generic with Renagel (EU) across phosphate concentrations from 1 to 40nM and then compared the two with 90% confidence intervals for the capacity constant (k_2). However the phosphate concentration range chosen by the sponsor did not encompass the maximum binding of phosphate as per the current August 2011 FDA guidance. The sponsor says this was because the study was designed against an older version of the FDA guidance document (August 2010) rather than the current version. The TGA was concerned about the impact this design flaw might have on the conclusion of equivalence between the proposed and innovator products.

To allay these concerns the sponsor provided a bridging study which examined phosphate binding at maximum phosphate concentration levels (up to 70 mM; 2 replicates only). The k_2 values for the test and reference products in this study appear to be similar (and slightly higher than the values derived in the initial study), however 90% confidence intervals for the T/R ratios were not calculated. The significance of these results in demonstrating equivalence between the test and reference products remains unclear.

For the kinetic binding study which is considered a supportive in vitro study, the sponsor demonstrated that both the generic and Renagel (EU) showed maximum phosphate binding was reached quickly however this test was performed using six replicates as per the older FDA guidance rather than the 12 replicates required by the current FDA guidance.

The PSC provided advice on this submission in May 2014 following the first round of evaluation (see *Quality findings* above).

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluator has recommended rejection of this generic sevelamer product due to the differences seen in the chemistry of the product not being addressed by any clinical data to demonstrate that the safety and efficacy of this generic would be the same as Renagel.

The clinical dossier did not include any clinical studies using this generic sevelamer product. The sponsor did provide an in vitro equilibrium study and an in vitro binding study along with a justification for not conducting a bioequivalence study. The two in vitro studies were evaluated by the quality evaluator and have been discussed above but the clinical evaluator has also provided a summary in the CER.

Pharmacology

The sponsor provided a justification for not conducting a bioequivalence study which the clinical evaluator has addressed. The evaluator notes the lack of systemic absorption and that any measurable levels of sevelamer would not be relevant. The sponsor states that it would be ethically problematic to conduct human studies when an internationally accepted in vitro alternative exists, however the evaluator has noted that this should not necessarily preclude some form of equivalence study being conducted given it is unknown what the clinical meaningfulness is of the differences observed between the generic and Renagel by the chemistry evaluator. The differences observed between healthy volunteers and patients imply that data from patients would be more relevant. It was noted that in vitro studies have been used internationally. The sponsor cited the use of the draft FDA guidance which has been available for a few years however the evaluator could not locate any generic sevelamer products that were registered by the FDA. The sponsor noted that it had a lodged a submission in Germany for this product however this is still under evaluation. The sponsor stated they had received correspondence from the Medicines and Healthcare products Regulatory Agency in the United Kingdom (UK) in which in vitro studies would be acceptable however the correspondence was not provided to the TGA. The sponsor referred to doses up to 14.4g of Renagel having been given without adverse effects and therefore any slight bioinequivalence would be low risk, which the evaluator commented that the long term effects of this in an elderly or unwell population are unknown. The clinical significance of the differences seen in the particle size specifications are unknown, however the quality evaluator has now resolved this matter.

No pharmacodynamic data were submitted but the evaluator has provided information in the CER on the pharmacodynamics of sevelamer from published literature.

Efficacy and Safety

No efficacy or safety data were submitted.

In summary the evaluator had concerns with:

a. The lack of clinical data to address the differences seen in the drug substance and the limited in vitro testing data.

b. The large size of the tablets and potential risk for obstruction. The sponsor indicated that the dimensions for length, breadth and thickness between the Renagel/Generic are as follows: 18.95 to 19.08/19.04 mm, 9.78 to 9.79/9.53 mm and 7.60 to 7.62/8.39 mm respectively. The evaluator comments that this represents a 6 to 7% increase in cross-sectional area.

c. The particle size which was resolved by further data submitted to the quality evaluator.

d. The cross-linking within the polymer with the potential for different phosphate or other anion binding and greater swelling which could lead to obstruction. The cross-linking in the generic product from testing of five further batches was 13.9 to 15% whereas in Renagel it was 10.6 to 20% (EU and Australian batches). It is unclear if this has clinical implications for binding different anions but the generic lies within the reference product's range and therefore is unlikely to be of significance.

Risk management plan

The TGA's PMSB has accepted the EU Risk Management Plan for Sevelamer GPPL, Sevelamer GxP, Seveligand, Phosligand, APO-Sevelamer, APOTEX-Sevelamer, Chemmart Sevelamer, GenRx Sevelamer, Terry White Chemists Sevelamer (sevelamer), version 1.0, dated September 2012, with the Australian Specific Annex (ASA), version 2.0, dated 25 March 2014.

The following were outstanding matters that should be followed up with PMSB and responded to in the Pre-ACPM Response:

- The sponsor should include the following important potential risk as an ongoing safety concern and consider appropriate pharmacovigilance and risk minimisation activities which should be reflected in an updated ASA: '*Swallowing difficulties and the potential for lodgement in the airway or upper gastrointestinal tract*.'
- The paediatric precaution in the PI should be amended to state: '*Sevelamer is not recommended in children below 18 years of age*.'
- A pre-dialysis statement in the PI should be considered: '*The safety and efficacy of sevelamer has not been established in predialysis patients*.'

The EU Summary of Product Characteristics (SmPC) mentions the possibility of folate deficiency during long term sevelamer treatment however the Australian PI does not include this information. The RMP evaluator recommends that additional monitoring of folic acid in patients undergoing peritoneal dialysis and during long term sevelamer treatment be considered for the PI.[17]

Risk-benefit analysis

Delegate's considerations

This submission is to register the first generic product of sevelamer, a non-absorbed, polymeric anion exchange resin that binds phosphate ions in the intestinal tract to manage hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease. This generic has not been registered overseas as yet but has been under evaluation in Germany since December 2012. The quality and clinical evaluators have recommended rejection and the PSC also recommended rejection. During the evaluation, the sponsor submitted further data to address the TGA's concerns and the TGA also had a meeting with the sponsor to discuss outstanding matters.

The Therapeutic Goods Act 1989, section 25, requires that when registering a new medicine, such as a generic medicine, the Secretary [or delegate] must evaluate the goods for registration having regard to, amongst other things:

> S25(1)(d): *whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established*;

From a quality perspective, the sponsor has not completely established the quality of the drug substance due to the differences in the total titratable amines and swell index that were observed in these tests. The 'total titratable amines' is a surrogate parameter and provides an indirect measure of its phosphate binding capacity. The level seen in the

[17] At 22 May 2015 the PMSB evaluator stated that 'All OPR [now PMSB] recommendations in relation to the above application have now been adequately addressed. Therefore if this application is approved the following specific condition of registration should be applied:
'The European Risk Management Plan (Version: 1.0 dated September 2012) with an Australian Specific Annex (Version: 3.0, dated 15 May 2014), must be implemented.'

generic product was lower than specified in the USP monograph and lower than demonstrated in the sponsor's own comparison with Renagel which suggests that having fewer free amine sites, although only marginal, may lead to a reduction in phosphate binding and therefore the efficacy of the product. The other parameter, swell index, is proportional to the extent of cross linking and inversely related to the free amine content. Free amine content is directly related to the phosphate binding capacity. The proposed swell index limits by the sponsor were not aligned with the USP monograph and were slightly higher. To address this concern the sponsor proposed a limit on the phosphate binding capacity of the drug substance to be closer to an acceptable level but was slightly less, implying that the phosphate binding capacity could be slightly less for this generic than Renagel. These slight differences in the drug substance raise concerns about the quality of the product and whether it is the same as Renagel such that its efficacy and safety would be the same. To try to address these concerns, the sponsor conducted studies examining phosphate binding capacity.

When registering a typical oral tablet, the sponsor normally submits a bioequivalence study to demonstrate the equivalence between the test and reference products that will then allow for the extrapolation of the safety and efficacy data from the reference product to the generic product to satisfy that safety and efficacy has been established for registration purposes.

For a non-absorbed locally acting product such as sevelamer, bioequivalence studies are not required since the product is not absorbed and therefore traditional bioequivalence studies cannot be used. This is noted in the Australian Regulatory Guidance for Prescription Medicines, Appendix 15, Section 2:

> *Applications to register or make changes to the types of products listed below need not normally be accompanied by biopharmaceutic data or a justification for not providing such data:*
>
> - *Products containing therapeutic substances which are not systemically or locally absorbed, for example, barium sulphate enemas oral suspensions, non-biodegradable ion exchange resins or other non-biodegradable long chain polymers, powders in which no ingredient is absorbed. If there is doubt as to whether absorption occurs, a study or justification may be required.*

Given that a biopharmaceutic study cannot be conducted then the submission must rely on convincing evidence from a chemistry perspective that this product is a generic of Renagel in terms of quality along with other data in lieu of the bioequivalence study to examine the phosphate binding capacity of this product, to ensure that the generic product will have the same safety and efficacy properties as the reference product, that is, Renagel.

For a generic medicine, there is no specific definition in the Act of a generic but in the Therapeutic Goods Regulations 1990, Schedule 9, Fees, Part 1 Interpretation of Table, 1 Definitions, a generic product is defined as follows:

> *Generic product means a medicine that, in comparison to a registered medicine or a medicine that has been registered but is no longer a registered medicine (previously registered medicine):*
>
> *a. has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine or previously registered medicine; and*
>
> *b. has the same pharmaceutical form; and*
>
> *c. is bioequivalent; and*
>
> *d. has the same safety and efficacy properties*

This definition can provide guidance as to what should be considered when registering a generic product, which is consistent with the TGA adopted guidances[18] but the decision that is taken by the Delegate is as displayed in s25(1)(d) of the Act.

The Investigation of Bioequivalence guideline states that '*a generic medicinal product is a product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the reference medicinal product, and whose bioequivalence with the reference medicinal product has been demonstrated by appropriate bioavailability studies.*' This definition is consistent with that in Schedule 9 of the Regulations but as noted, normal bioequivalence studies cannot be conducted with this type of product, therefore alternative data in lieu of this needs to be provided. To assist with this, the TGA has adopted a guidance for locally acting products that is discussed below.

The TGA adopted guidance called '*Note for guidance on the clinical requirements for locally applied, locally acting products containing known constituents*' provides further information on what should be expected for products that are not systemically absorbed. Although this guidance was adopted in 1996 by the European Medicines Agency (EMA), it concerns locally acting products which are applied locally and exert their effect at the site of action with systemic action being an undesired effect. This guidance provides examples of dermatological products, inhalation products, eye drops, ear drops, nasal products and orally applied products which act locally. Whilst it can be argued as to whether this guidance can be applied to this type of product, sevelamer is nevertheless a locally acting product which is not systemically absorbed and therefore this guidance has relevance. The guidance states that it is necessary for locally acting products that a generic is therapeutically equivalent to the product already approved, that is, both products are equivalent in terms of efficacy and safety. To demonstrate this, clinical equivalence studies can be used or depending on the situation, human pharmacodynamic studies or animal or in vitro studies can be used provided they are validated. The sponsor has not conducted a therapeutic equivalence study or a human pharmacodynamic study but has chosen to conduct two in vitro studies as per another guidance document from the FDA (FDA Draft Guidance on sevelamer hydrochloride, August 2011) which has not been adopted by the TGA. This latter approach, however, does not provide evidence of efficacy and safety of the product in humans but seeks to establish the 'bioequivalence' of the generic and reference via in vitro studies so as to then be able to extrapolate the efficacy and safety from Renagel. Herein lies one of the issues to consider; whether this approach by the FDA which has not been adopted by the TGA, is an acceptable and validated surrogate for conducting some form of clinical study with this generic compared with Renagel to establish that the two products are equivalent. The TGA accepts that this approach has merit but the sponsor did not fully complete the studies as recommended in this FDA guidance.

The FDA guidance has not been adopted by the TGA but has relevance since it directly discusses the acceptable evidence to submit to support the conclusion of bioequivalence between generic and reference sevelamer products. The guidance, when registering a generic medicine, recommends two in vitro studies be conducted: an in vitro equilibrium binding study which should be repeated at least 12 times that includes a binding constant with 90% confidence intervals calculated (80 to 120%) and an in vitro kinetic binding study again repeated 12 times but with 90% confidence intervals not being required. Unfortunately the version of the guidance used by the sponsor to support their submission was an older version from August 2010 which was current when the studies were conducted (September 2010 to January 2011) but not current when the submission was lodged with the TGA. The current version from August 2011 has amended requirements that have not been fully met by the sponsor. The difference in the two versions of this

[18] Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev1) and ARGPM, Appendix 15.

guidance relates to the phosphate concentration range and the number of replicate studies required. In the earlier version of the guidance, the phosphate concentration range to be assessed was 1 to 40nM whereas in the current version it requires a range that ensures maximal binding was achieved. In the earlier version of the guidance, the number of times the two in vitro studies had to be repeated was '*an adequate number of replicates should be used for each set of conditions*' which the sponsor did to six replicates whereas the current guidance states that 12 replicates should be conducted for each study. To address these matters the sponsor examined phosphate binding at the maximum concentration levels (up to 70nM) but only did two replicates. Thus the sponsor did not conduct 12 replicates up to the maximum phosphate concentration levels as recommended by the guidance but instead did six replicates up to 40nM and 2 replicates up to 70nM. For the kinetic study, the sponsor also only did six replicates rather than the 12 replicates as recommended by the FDA guidance. By not fully completing the in vitro testing requirements in the FDA guidance, then this increases the probability that the results may be due to chance rather than being true results and therefore do not completely allay the concerns observed regarding the differences in titratable amines and swell index and whether there is a different (possibly lower) phosphate binding capacity of this generic product compared to Renagel.

The clinical evaluator had two concerns that remain: the size of the tablets and the lack of clinical data to address the differences seen in the chemistry data in terms of the drug substance and the limited in vitro testing that were conducted. It is noted that both the Renagel and this generic sevelamer are large tablets with about the same length (19 mm), slightly less width for the generic by about 0.26 mm and slightly greater thickness by about 0.79 mm. Whilst there is no clinical data to know if these differences are likely to be significant, it is probably unlikely but the PI should nevertheless provide warnings on the size of the tablets and risk of choking/obstruction. The sponsor has also provided samples and a video of the tablet's disintegration which indicate disintegration at a similar time to Renagel.

In summary, there are a few concerns with this submission. Firstly, this generic medicine has not been administered to any people as yet, thus some form of clinical data such as a pharmacodynamic study would have provided reassurance that the differences seen in the drug substance or the deficiencies in the in vitro studies were not clinically significant to its ability to lower phosphate levels. Given it has not been registered anywhere overseas yet then there is also no clinical experience with this generic product to provide reassurance on its efficacy and safety. Secondly, the TGA adopted guideline on locally acting products allows for an in vitro study to be conducted instead of a clinical equivalence study or pharmacodynamic study, however an in vitro study is a surrogate method of establishing equivalence in lieu of a clinical study. The concern here is that the sponsor conducted two in vitro studies that did not provide sufficient reassurance that the phosphate binding capacity of this generic was equivalent to Renagel since they did not do a sufficient number of repeat tests and that phosphate binding at the maximum concentration used in the studies was only assessed in two replicates instead of the required twelve and did not include 90% confidence intervals. The reduced testing and lack of confidence intervals reduces the confidence in concluding that the generic and reference are equivalent and thus the ability of the Delegate to conclude that efficacy and safety can be extrapolated through this method of assessing 'bioequivalence'. The FDA guidance, although not adopted by TGA, was relied upon by the sponsor to support their submission however the sponsor did not meet its current requirements. Thirdly, the differences observed between the generic and Renagel by the quality evaluator in terms of total titratable amines and swell index suggests that this generic substance is of different quality to Renagel and therefore the phosphate binding capacity, that is, efficacy, of this generic may be different. The lack of human data or convincing in vitro data means that the differences observed by the quality evaluator cannot be alleviated. Thus, there is doubt

that the drug substance in this generic is the same as Renagel due to the differences in total titratable amines and swell index, the in vitro studies were not conducted in full to provide convincing evidence of the 'bioequivalence' of this generic with Renagel and there is no clinical study to alleviate these concerns such that efficacy and safety can be satisfactorily established to support registration.

Having noted these concerns, phosphate levels can be easily measured in a patient prescribed this generic and can be monitored over time such that to some extent these small differences between the generic and reference in terms of the drug substance and the deficiencies in the testing program conducted may not be clinically significant. However when registering a generic medicine it is important to remember that the safety and efficacy properties of both the generic and reference should be the same, noting that the products can be interchanged. Unfortunately it is unknown whether this is the case given there are no clinical data and the in vitro data supplied was insufficient to conclude that this generic and Renagel are bioequivalent.

RMP

The sponsor should address the outstanding RMP matters.[17]

Data deficiencies

No clinical studies and a lack of sufficient testing as recommended by the FDA in its guidance for demonstrating bioequivalence between a generic sevelamer and reference.

Conditions of registration

The following are proposed as conditions of registration, should this product be approved:

> The implementation in Australia of the EU Risk Management Plan for Sevelamer GPPL, Sevelamer GxP, Seveligand, Phosligand, APO-Sevelamer, APOTEX-Sevelamer, Chemmart Sevelamer, GenRx Sevelamer, Terry White Chemists Sevelamer (sevelamer), version 1.0, dated September 2012, with the Australian Specific Annex, version 2.0, dated 25 March 2014, and the RMP agreements from the Pre-ACPM Response of [date], included with submission PM-2013-00742-1-3, and any subsequent revisions, as agreed with the TGA.

Summary of issues

The primary issues with this submission are as follows:

1. Whether the medicine has the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in Renagel.
2. Whether the sevelamer hydrochloride used in this product binds phosphate in an equivalent manner to Renagel and therefore has the same safety and efficacy properties.
3. Whether further studies, be they in vitro or clinical , are required to support the registration of a generic sevelamer.

Proposed action

The Delegate was not in a position to say, at this time, that the application for Sevelamer GPPL, Sevelamer GxP, Seveligand, Phosligand, APO-Sevelamer, APOTEX-Sevelamer, Chemmart Sevelamer, GenRx Sevelamer and Terry White Chemists Sevelamer should be approved for registration.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Does this generic product contain the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in Renagel?
2. Are the differences observed in the drug substance (total titratable amines and swell index) of clinical concern that this generic may not have the same safety and efficacy properties as Renagel?
3. Has sufficient data been presented from the in vitro studies to demonstrate equivalence between this generic and Renagel or should the sponsor undertake further testing?
4. Should the sponsor conduct some form of clinical study such as a pharmacodynamic study to support the efficacy and safety of this generic compared with the reference?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Questions for the sponsor:
The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Is the sponsor intending to conduct any further *in vitro* testing consistent with the FDA guidance on sevelamer?
2. Is the sponsor intending to further refine the specifications so that the total titratable amines and swell index will comply with the draft USP monograph?
3. What is the current status of the submission in Germany, have any concerns been raised regarding this submission and when is an outcome expected?

Has this generic product been registered anywhere globally and if so, are any postmarket data available?

Response from sponsor

Regulatory approval of generic products without bioequivalence or other in vivo data in humans is now commonplace in Australia and other comparable regulated markets. Since the development of the Biopharmaceutical Classification System (BCS) in the USA about 20 years ago, many products have been able to obtain a waiver from the requirement to provide such human data as part of the data package and have been approved on chemistry and manufacturing data alone.

Biowaivers under the BCS are now included in both FDA and EU bioequivalence guidelines; the EU guideline has been formally adopted by TGA. TGA has approved a number of such products using a BCS biowaiver without bioequivalence or other in vivo data over recent years, including a number of applications sponsored by Generic Partners. These products are given Pharmaceutical Benefit Scheme (PBS) listing and can be marketed to patients without prior clinical experience in humans.

One purpose of such waivers (as discussed in the US Code of Federal Regulations) is to reduce the need for unnecessary in vivo clinical trials and exposure of human subjects to unnecessary risks, when alternatives are available that allow a conclusion of bioequivalence to be made.

In this case, the US FDA has provided a recommendation that bioequivalence of generic sevelamer products can be adequately demonstrated using an in vitro phosphate binding assay in place of the human bioequivalence study normally required for approval of generic products. The rationale for this is that sevelamer is an insoluble, non-absorbed ion-exchange polymer that is taken orally to chemically bind phosphate in the

gastrointestinal (GI) tract and thereby prevent phosphate being absorbed into the systemic circulation. As the drug is not absorbed, it has no systemic action.

This approach is not unique to sevelamer, with other drugs (such as cholestyramine and lanthanum carbonate) that act with the GI tract also having recommendations from the FDA that bioequivalence can be demonstrated by in vitro binding studies analogous to that recommended for this product.

This approach is also consistent with published TGA guidelines. TGA Guidance 15: Biopharmaceutical Studies, which states that biopharmaceutical data is not required for medicines that are not systemically or locally absorbed and specifically refers to 'nonbiodegradable ion-exchange resins' and 'other non-degradable long chain polymers'.

In this application, the sponsor demonstrated that the in vitro phosphate binding of the proposed generic sevelamer hydrochloride tablets is equivalent to the innovator Renagel and therefore the two products can be taken to be clinically equivalent. Consistent with the requirements of the US FDA, an agency with comparable regulatory standards to the TGA, further clinical studies should therefore not be required and could be perceived to be unethical in view of appropriate in vitro testing methods being established.

In addition to the current application to the TGA, the same generic product has been submitted by a product manufacturer in Germany, using an identical data package as submitted to the TGA. Although questions have been received, the German agency has not raised any issues in relation to the in vitro equivalence approach or the conduct of the in vitro studies with the sponsor; these questions have been shared previously with TGA. It is also worth noting that USV has also submitted an application for the alternative salt form, sevelamer carbonate which is based on a comparable in vitro equivalence strategy and dataset and this application has been accepted and is currently under review by the FDA.

Quantitative composition of therapeutically active substances and similar quality to Renagel

One of the main concerns highlighted by the TGA is the quantitative composition of the therapeutically active substances in the generic product and whether the substances are of similar quality to those used in Renagel. Specifically, the issue was regarding slight differences in the specifications proposed for titratable amines and swell index tests.

The sponsor accepts the quality evaluator's conclusion that '*the only way to ensure equivalence between the proposed and reference products was if their respective drug substance and drug product specifications were matched*'.

In response, the sponsor would like to inform the TGA and ACPM that the manufacturer, has agreed to adopt the titratable amines and swell index limits to comply with the draft USP monographs. With these specification revisions (discussed in more detail below), the proposed generic active substance and drug product will be fully compliant with all the tests included in the draft USP monograph.

The manufacturer will also revise the specification limit for phosphate binding in accordance with the TGA's request. The phosphate binding capacity test is not mandated by the draft USP monograph but its inclusion as a routine quality control provides additional assurance of the quality of the drug substance and product with respect to its key quality and clinical parameter.

In adopting the draft USP monograph specifications, the quantitative composition of the generic product will be the same quantitative composition of therapeutically active substance and therefore be of similar quality to Renagel. Furthermore, in adopting the draft USP limits for titratable amines and swell index it is reasonable to predict the generic product will also have the same safety and efficacy properties as the reference. This assumption is also made for all generic drugs for which bioequivalence testing is conducted in small numbers of patients.

Drug substance swell index

The drug substance specification for swell index will be tightened to match the draft USP monograph limit of 6.2 to 8.4 on the dried basis. Available batch analytical data demonstrates that the drug substance can comply with this quality control limit.

It should be noted that the swell index test is not a measure of the extent of swelling of the sevelamer particles in the drug substance. That is, a swell index result of, say 8.0, does not mean that the swollen drug substance particles are eight times larger than the unswollen ones. Rather, the swell index is the ratio of the increase in mass of the drug substance saturated with water to the weight of the original dry drug substance and is more a measure related to drug substance crosslinking.

Titratable amines

The level of titratable amines will be tightened to match the limits of 11.3 to 14.1 mmol/g indicated in the draft USP monograph for the drug substance and the drug product. The identical limits for the drug substance and the drug product reflect the high proportion of active substance which constitutes the dose form. Due to the current absence of an independent compendial reference standard, a minor amendment to the unit of expression for the drug product limits has been agreed with the TGA whereby the level of titratable amines for the drug product will be expressed as an absolute value (mmol/g) rather than a percentage of a reference standard as recommended in the draft monograph. Batch analytical data for titratable amines demonstrates that batches of the generic product can be manufactured to comply with the draft monograph. Importantly, the batch characterised in the in vitro binding studies and included in the TGA submission meets the draft USP monograph limits. While a number of the batches manufactured to date are towards the lower USP limit for this parameter, the product manufacturer is able to select drug substance batches specifically to ensure these limits will be met for all batches supplied to the Australian market.

Phosphate binding capacity

The manufacturer accepts the TGA's recommendation to revise the limits for phosphate binding capacity to 5.2 to 6.4 mmol/g for the drug substance and drug product. Batch analytical data demonstrates that the manufacturer can comply with these limits. As discussed in relation to titratable amines, as multiple drug substance batches are combined to manufacture finished product tablets, the manufacturer can select drug substance batches to ensure phosphate binding characteristics comply with the specification limits.

Phosphate binding and equivalence to the innovator product

In demonstrating that the generic product binds to phosphate in an equivalent manner to Renagel, it is helpful to consider the mechanism of binding.

Phosphate binding to the active substance is chemical in nature involving electrostatic interactions and hydrogen bonding. In context of the simple chemical and diffusional nature of the binding interactions with the target phosphate, prediction of clinical efficacy using in vitro techniques is the most direct method for assessing equivalence for this non-systemically absorbed active substance. Given the tablets act locally within the gastrointestinal tract, disintegration of the tablets in the aqueous environment is the main prerequisite for binding and the generic tablets have been demonstrated to disintegrate rapidly approximately within 6 to 10 minutes.

The original in vitro bioequivalence studies included in the application were conducted between September 2010 and January 2011. The studies were conducted in accordance with the August 2010 FDA Draft Guidelines in place at the time of the study. It is common practice for authorities to accept data generated in accordance with the current guideline at the study initiation. The differences between the earlier version (August 2010) and the

current version (August 2011) are minor and the sponsor does not consider that repeating the studies would provide additional information or affect the conclusion of equivalence demonstrated by comparable phosphate binding of the reference and generic product.

The methods described in the two guidelines are essentially the same, with two differences:

- The earlier 2010 guideline states that a phosphate concentration range of 1 mM to 40 mM should be used in the study, while the more recent 2011 guideline does not include a recommended concentration range, only that it should be ensured that maximal binding has been achieved;
- The 2011 guideline states that 12 replicates should be used at each test point, while the earlier 2010 guideline did not specify the number of replicates required.
- The phosphate concentration range of 1 mM to 40 mM used in the submitted study as defined by the August 2010 version of the FDA guidance. This concentration range is also consistent with the concentration range of 1 mM to 38.7 mM referenced in the paper published by Swearingen (2002)[19], upon which the FDA draft guideline methodology is based.

Although it appeared that saturation had been reached by 40 mM phosphate concentration, in response to a TGA question on this issue, a bridging study was performed to understand the impact of extending the concentration range further up to 70 mM. These additional studies indicated that the level of bound phosphate does not significantly increase above 40 mM such that the sponsor was confident that the maximal binding was encompassed by the original experimental design and confirming the validity of the results of the original study as performed.

The pivotal parameter for assessment of bioequivalence (k_2) is calculated from a Langmuir plot using the gradient of the graph comparing the unbound/bound phosphate ratio to the unbound concentration. Importantly, both graphs (over 1 to 40 mM and 1 to 70 mM) have very similar gradients and therefore gave comparable k_2 values. This provides clear evidence that extending the concentration range to 70 mM has little effect on the results of the study and the results of the original study as submitted stand valid. This bridging study was submitted to the TGA in the Milestone 5 Response.

The use of 6 replicates was consistent with published studies at the time this study was conducted, although the FDA guideline did not specify the number required. Although the updated guideline stated that 12 replicates were to be used, the sponsor believes that this change would have little effect on the study and the results can still be considered valid. In general, the width of a confidence interval is inversely proportional to the square root of the number of replicates used, such that the larger the number of replicates, the higher the study power and the narrower the confidence interval observed. Therefore, although the change in the number of replicates would not be expected to have a significant effect on the results of the study, if anything the use of 12 replicates would result in a study more likely to show equivalence than the one presented in this application.

The sponsor believes that the slight differences between the two FDA guidelines do not affect the conclusions of the phosphate binding study provided to TGA and the products can be considered equivalent on that basis. It should also be noted that the level of titratable amines for the generic product batch included in the in vitro equivalence studies was compliant with the draft USP monograph which also confirms an equivalent quantitative composition between the two products.

[19] Swearingen RA, Chen X, Petersen JS, Riley KS, Wang D, Zhorov E; J. Pharm. Biomed. Anal. 29 (2002) pp 195–201

Global regulatory status and post-market experience

An identical dossier has been submitted in Germany as a national application which is currently under review. Unlike Decentralised Procedures which typically involve a number of European member states and require a formal assessment timelines to coordinate activities, German national procedures do not have a formal assessment timeline. However, as noted above, although questions have been received from the German agency, no issues have been raised concerning the conduct or results of the comparative phosphate binding study.

An application for Sevelamer carbonate, with bioequivalence based similarly on an in vitro phosphate binding study, has been submitted to the FDA.

The manufacturer, has an identical product approved and currently on the market in India (March 2008) and Uruguay (January 2014). No formal pharmacovigilance monitoring occurs in these markets but there have been no anecdotal reports of adverse effects to the manufacturer.

Conclusion

Registration of generic products without human studies is not uncommon, with BCS Class I and Class III products being registered routinely in regulated markets without in vivo data and FDA recommendations for a number of locally acting, non-absorbed locally acting products (including sevelamer) for bioequivalence is based on in vitro binding studies alone.

The current application references these TGA and international in vitro approach precedents for demonstrating equivalence to the innovator product. The equivalence of the generic product and the innovator product has been demonstrated using in vitro studies performed in accordance with the FDA guidelines for sevelamer hydrochloride. Despite some minor differences between the previous version of the FDA guideline and the current FDA recommendation, the sponsor considers that the results can still be considered robust and acceptable to demonstrate equivalence of the proposed generic product and Renagel. Performing further in vitro studies would not provide additional information or change the conclusion. Furthermore, the conduct of clinical studies would not be justified and unethical in the context that internationally recognised in vitro techniques are in existence.

The sponsor acknowledges the concerns raised by the quality evaluator and the generic manufacturer has agreed to amend their specifications in accordance with the USP monograph. Adopting the same specifications as the innovator product will ensure that the quantitative composition and quality of the generic product is the same as Renagel.

Although the generic and Renagel tablets are equivalent in size, swallowing and the potential for choking may be a safety issue for both of these large tablets. In response, the sponsor is willing to amend the PI and Consumer Medicine Information (CMI) in line with TGA's advice to ensure this risk is minimised. It should be noted that the current generic product's PI texts have been amended to include the most recent approved safety changes for Renagel.

The sponsor has in place a RMP with an ASA to manage safety risks and to enhance routine pharmacovigilance activities. The RMP has been accepted by the TGA and will be revised to include the approved PI and CMI as attachments.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new generic medicine.

The ACPM resolved to recommend to the TGA Delegate of the Minister and Secretary that:

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the delegate that Sevelamer GPPLl Sevelamer GXP, Seveligand, Phosligand, APO-Sevelamer, Apotex-Sevelamer, Chemmart Sevelamer, Genrx Sevelamer, Terry White Chemists Sevelamer film coated tablets containing 800 mg of sevelamer hydrochloride has an overall negative benefit-risk profile for the proposed indication.

The ACPM concluded that the evidence did not satisfactorily establish the same quantitative composition of the generic sevelamer compared to the innovator product and in the absence of safety and efficacy data it is not possible for the generic to assume the safety and efficacy profile of the innovator.

In making this recommendation the ACPM:

- Noted that the sponsor has agreed to adopt the titratable amines and swell index limits to comply with the draft USP monographs and has also agreed to revise the limits for phosphate binding capacity.
- Noted that the sponsor did not conduct a therapeutic equivalence study or a human pharmacodynamic study, but has chosen to conduct two in vitro studies as per a guidance document from the FDA (FDA Draft Guidance on sevelamer hydrochloride, August 2011), which has not been adopted by the TGA.
- Noted the in vitro bioequivalence studies had an insufficient number of repeat tests, although they were in line with the FDA requirements at the time, and that the implications with respect to phosphate binding are uncertain.
- Advised that the only way to provide absolute assurance that the drug was equivalent to the innovator was to conduct a clinical study to support the efficacy and safety of this generic compared with the reference product.

Specific Advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does this generic product contain the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in Renagel?

The ACPM considered that in the submitted data there were differences in quantitative composition of the proposed product, such as titratable amines, swell index and the number of replicates used in the bridging study to determine the level of bound phosphate. However, the ACPM noted that the sponsor has agreed to adopt the titratable amines and swell index limits to comply with the draft USP monographs. The sponsor also stated that it would revise the specification limit for phosphate binding. The ACPM agreed that the proposed product may have similar composition to the innovator product with these modifications.

2. Are the differences observed in the drug substance (total titratable amines and swell index) of clinical concern that this generic may not have the same safety and efficacy properties as Renagel?

The ACPM considered that the impact on the safety and efficacy of differences observed in the drug substance (prior to receiving the sponsor's pre-ACPM response) was not completely known and that without a clinical study are uncertain.

3. Has sufficient data been presented from the in vitro studies to demonstrate equivalence between this generic and Renagel or should the sponsor undertake further testing?

The ACPM noted biopharmaceutic data are not required by the TGA for medicines that are not systemically or locally absorbed. However, the TGA guidelines do not state that no clinical data are required. The ACPM noted that the FDA will accept bioequivalence of these products if demonstrated by in vitro binding studies, data which the sponsor has submitted. The ACPM noted that the sponsor's study was in line with the FDA requirements at the time but the FDA Guideline is not adopted by the TGA and has since been updated. The ACPM was concerned about the limited number of replications and the impact they might have on the conclusion of equivalence between the proposed and innovator products. The ACPM considered that there is therefore still some doubt regarding the equivalence of the two products.

4. Should the sponsor conduct some form of clinical study such as a pharmacodynamic study to support the efficacy and safety of this generic compared with the reference?

The ACPM noted that the sponsor has not conducted a therapeutic equivalence study or a human pharmacodynamic study, but has chosen to conduct two in vitro studies as per a guidance document from the FDA (FDA Draft Guidance on sevelamer hydrochloride, August 2011), which has not been adopted by the TGA. The ACPM considered that although the sponsor has agreed to adopt the titratable amines and swell index limits to comply with the draft USP monographs and will revise the specification limit for phosphate binding, the only way that there can be assurance that the proposed product acts the same as the innovator is by conducting a clinical study. The ACPM noted that not all patients taking this medication are severely ill, as suggested by the pre-ACPM response, with some continuing to work, and that it would be possible to conduct a clinical study in this population.

Initial outcome

Based on a review of quality, safety and efficacy, TGA rejected the registration of Sevelamer GPPL/Sevelamer Gxp/Seveligand Phosligand/APO-Sevelamer/Sevelamer Apotex/ Chemmart Sevelamer/ Genrx Sevelamer/Terry White Chemists Sevelamer

The Delegate notes that the 400 mg tablet initially included in the application was withdrawn as stated in the data enclosed with the company's email dated 20 May 2014, so from here all of the following, and the term the goods, only refer to the 800 mg tablet, indicated for:

'*For the management of hyperphosphataemia in adult patients with Stage 4 and 5 chronic kidney disease*'

Reasons for decision

Quality

There are draft USP monographs for Sevelamer Hydrochloride and Sevelamer Hydrochloride Tablets. In an iterative process up to and including the Pre-ACPM response, the sponsor has amended their specifications of the drug substance and the finished product to align with the requirements of these draft monographs.

Though some batches of the drug substance failed to meet the final limits for phosphate binding capacity (5 of 22 results were low), chloride content (3 of 22 results were low) and titratable amines (9 of 14 results were low), the sponsor has stated that it will pick batches such that the product supplied to Australia will meet the accepted limits.

Sufficient other quality data were also included in the dossier and subsequent correspondence.

The Delegate therefore accepts that the proposed drug substance and drug product are of adequate quality.

Efficacy

The sponsor has argued throughout that just matching certain parameters relating to the drug substance and the drug product to those of the Australian Reference product and performing the phosphate binding studies as stipulated in the FDA Draft Guidance of August 2010 should be sufficient to register the product.

This premise is not accepted for a number of reasons (in no order of merit).

a. The FDA guidance is still draft, is stated to contain nonbinding recommendations (so that even if all the criteria are met the FDA may still decide not to register), and this guidance has not been adopted by the TGA.

b. Though the sponsor now agrees to match the draft USP monograph requirements for the drug substance and drug product and the quality is acceptable, the results of some parameters were different for the goods compared to the Australian Reference product and some batches would not have met the draft USP monograph requirements.

c. Further the nature of the drug substance is such that differences in the method of manufacture may lead to differences in the 3D structure (which cannot be controlled by the routine quality control tests) that may lead to the proposed product having a different safety and efficacy compared to the Australian Reference product. This is borne out by the most recent (December 2014) version of the FDA draft guidance that is the first version to refer to applying to generic products and includes two pages of data required to demonstrate the chemical equivalence of drug substances from different sources.

d. The phosphate studies performed by the sponsor (and in particular the equilibrium studies) were only repeated for 6 replicates and only to a phosphate concentration of 40 mM. This was the requirement in the August 2010 version of the FDA guidance. However this requirement was changed in later versions to the performance of 12 replicates to a phosphate concentration such as to encompass the maximum phosphate binding concentration.

e. Though some data to a phosphate binding concentration of 70 mM were provided, the Delegate accepts the advice of the PSC that because of the apparent variability, 12 replicates to a phosphate concentration which clearly shows maximum binding would be required.

f. The TGA clinical evaluator and the ACPM concluded that it can only be assured that the proposed product acts the same as the innovator is by conducting a clinical study.

   This is consistent with the EU Guidance adopted in Australia (CPMP/QWP/239/95) and the approach taken in Europe where the first generic product of sevelamer carbonate tablets was approved in 2014[20]. The news item for this event clearly indicated that a Phase III safety and efficacy study was required for this approval: '*as sevelamer is a polymer that is not absorbed from the gastro-intestinal tract, a conventional bioequivalence study is not possible for this product. Synthon's clinical equivalence study was set up following Scientific Advice from several European regulatory authorities'*.

[20] http://www.synthon.com/Corporate/News/PressReleases/Synthon-obtains-European-approvals-for-sevelamer?sc_lang=en

Thus the Delegate concludes that a clinical study is required to demonstrate the efficacy of the proposed 800 mg goods.

Safety

For the same reasons mentioned under efficacy above, the Delegate concludes that a clinical study is required to demonstrate the safety of the proposed 800 mg goods. In particular, the clinical evaluation points out that a known adverse event of the Australian Reference product is related to the decrease in systemic bicarbonate ions (the drug substance may bind bicarbonate ions as well as phosphate ions) and no data was provided to demonstrate that the goods will not lead to lower systemic levels of bicarbonate.

Conclusion and decision

For the reasons set out above, the Delegate decided not to register the goods because the safety and efficacy of the goods has not been satisfactorily established.

Following the initial decision described above, the sponsor sought a review under the provisions of Section 60 of the Therapeutics Goods Act.

Final outcome

The Delegate of the Minister for the review noted that paragraph 25(1)(d) of the Therapeutic Goods Act, which requires the goods to be evaluated with regard to whether the quality, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established, is of particular relevance.

The following is an excerpt from the Delegate of the Minister's report:

Concerns regarding the quality of the product were resolved. The outstanding issues concern therapeutic equivalence and safety of the product proposed for registration. There is no clinical evidence to support therapeutic equivalence or safety of the product proposed for registration on the ARTG.

The sponsor has claimed that matching certain parameters relating to the drug substance and the drug product to those of the Australian Reference product and performing the phosphate binding studies as stipulated in the FDA Draft Guidance of August 2010 should be sufficient to register the product.

It has not been made clear to the TGA why that FDA document should be the basis for a conclusion of therapeutic equivalence. The FDA document Draft Guidance on Sevelamer Hydrochloride (2010) is a draft document and has since been superseded by another draft FDA document. These FDA guidelines include the statement that '*This draft guidance, once finalized will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It is a draft and does not create or confer any rights for or on any person and does not operate to bind the FDA or the public*'. Additionally the recommendations for equilibrium binding studies in those guidance documents were not fully met in the submitted data.

The sponsor has not demonstrated that the sevelamer product proposed for registration has the same 3-dimentional structure as the reference product. Therefore the product may not be therapeutically equivalent to the reference product and the safety profile may differ from that of the reference product.

Differences in phosphate binding between the product proposed for registration and the reference product also suggest that the products may not be therapeutically equivalent and that there may be differences in safety between these products. While some samples of the product proposed for registration have shown the same phosphate binding profile as the reference product on in vitro testing, it is not known whether the binding sites will

act in the same way for other molecules in vivo. The Delegate has particular concern that the binding of bicarbonate ions may differ from that of the reference product. Differences in bicarbonate binding could affect the incidence of metabolic acidosis, a condition to which patients with chronic renal failure are vulnerable.

The TGA has issued guidance via adopted EMA documents and Guidance 15: Biopharmaceutic studies Version 1.1(previously ARGPM 15 Biopharmaceutic studies) to provide recommendations on the data that should be submitted to support registrations of these types of therapeutic goods that is locally applied, locally acting products. The recommendations in that guideline have not been adequately met.

Conclusion and decision

Therapeutic equivalence between the reference product and the safety of the product proposed for registration has not been demonstrated. Therefore the Delegate has decided to confirm the initial decision on the basis that safety and efficacy of the product proposed for registration on the ARTG have not been satisfactorily established.

Outcome from appeal to the Administrative Appeals Tribunal (AAT)

The sponsor appealed to the Administrative Appeals Tribunal (AAT) for review of the TGA's decision not to register Sevelamer.

The sponsor later withdrew their application to the AAT.

Attachment 1. Extract from the Clinical Evaluation Report

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